CONTENTS

The American Journal of Medicine

VOL. III SEPTEMBER, 1947 No. 3

Editorial

Clinical Studies

An extensive and well documented study of the place of penicillin aerosol inhalation therapy in the medical management of bronchiectasis, lung abscess and chronic suppurative bronchitis. Improvements in the technic of administration, in dosage schedules, and the combined use of penicillin by other routes and of other antibiotics are described. High local concentrations and therapeutic blood levels of penicillin could be attained with encouraging clinical results in the patients treated.

A simple apparatus is proposed as a portable unit for aerosol medication in the home.

Dr. Loveless has attempted to evaluate objectively the efficacy of benadryl and pyribenzamine in a variety of disorders, chiefly allergic, by an analysis of published reports and of her own experience. The relative incidence of side reactions is also estimated.

An analysis of the results obtained with benadryl in the authors' series of asthmatics. Seven of the thirty patients tested reported symptomatic relief.

A discussion of the rickettsias, with special reference to the American form of typhus fever (Brill's disease). Two cases are described in which the clinical course suggested and skin biopsy confirmed the diagnosis of rickettsial disease, despite failure to obtain additional evidence by serologic methods.

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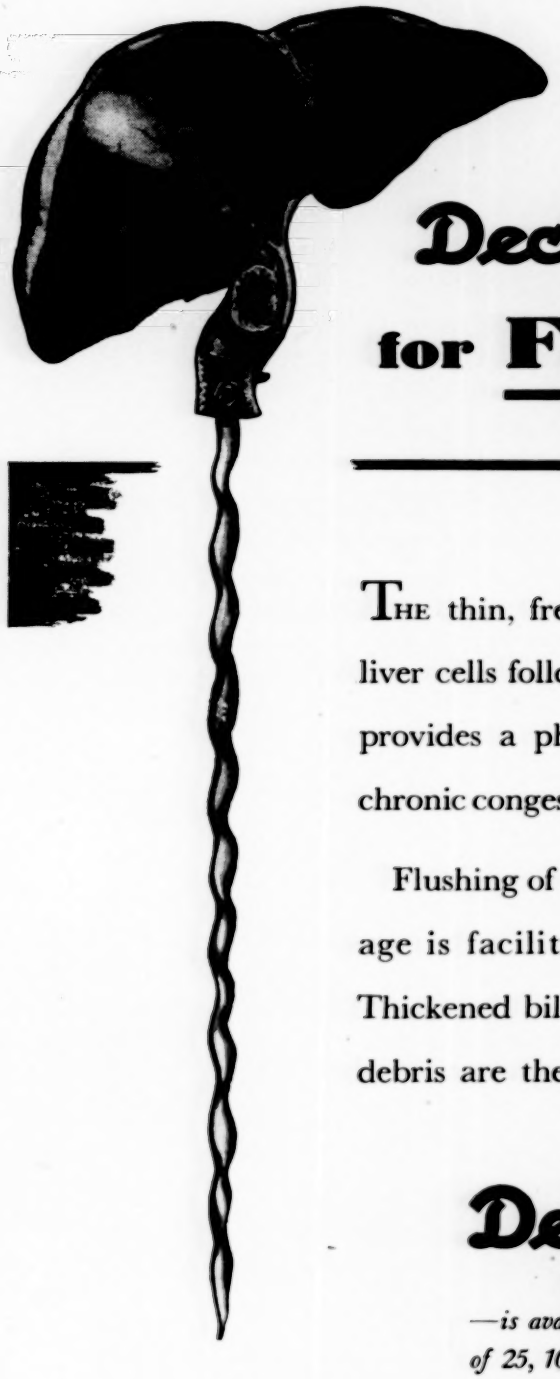

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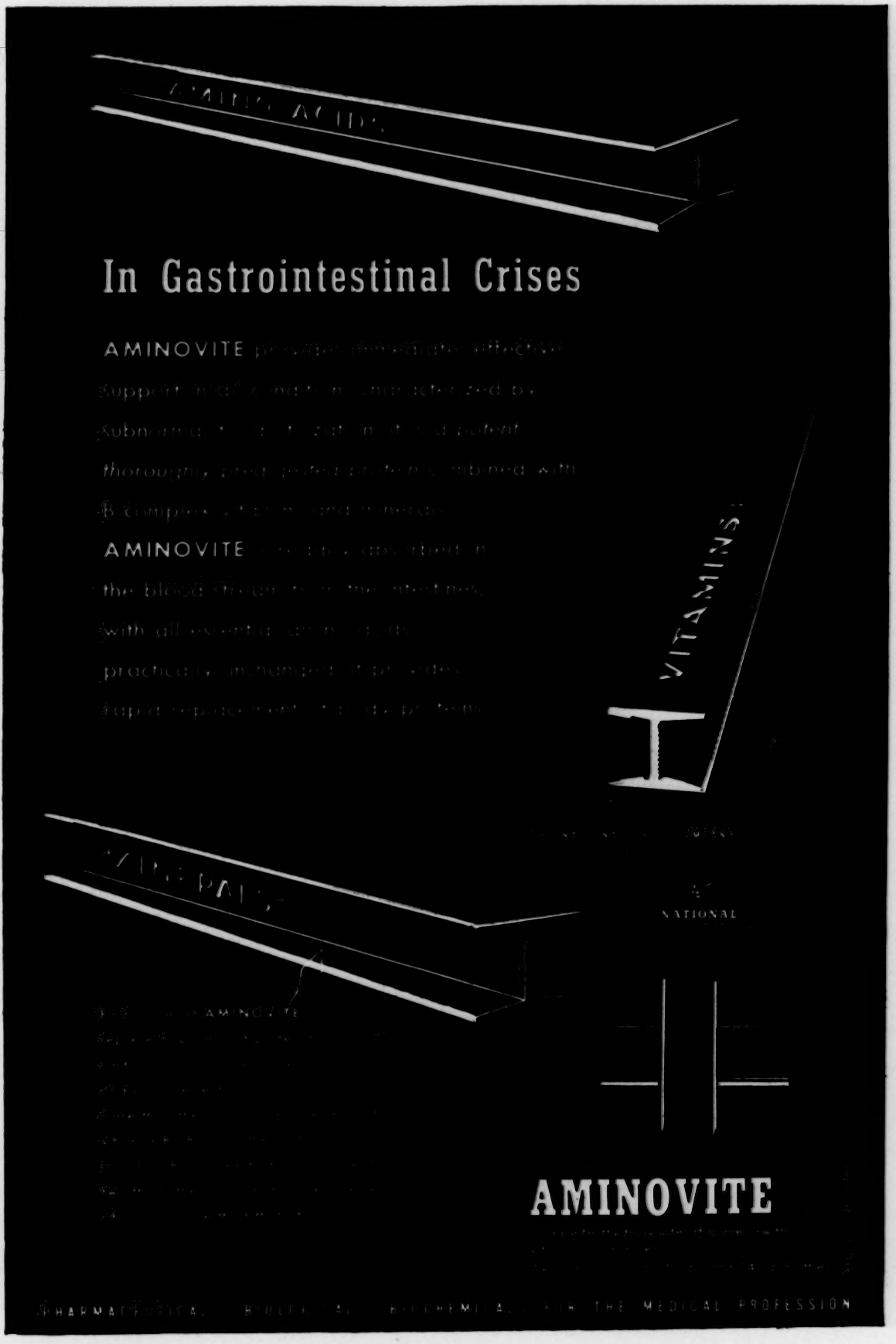
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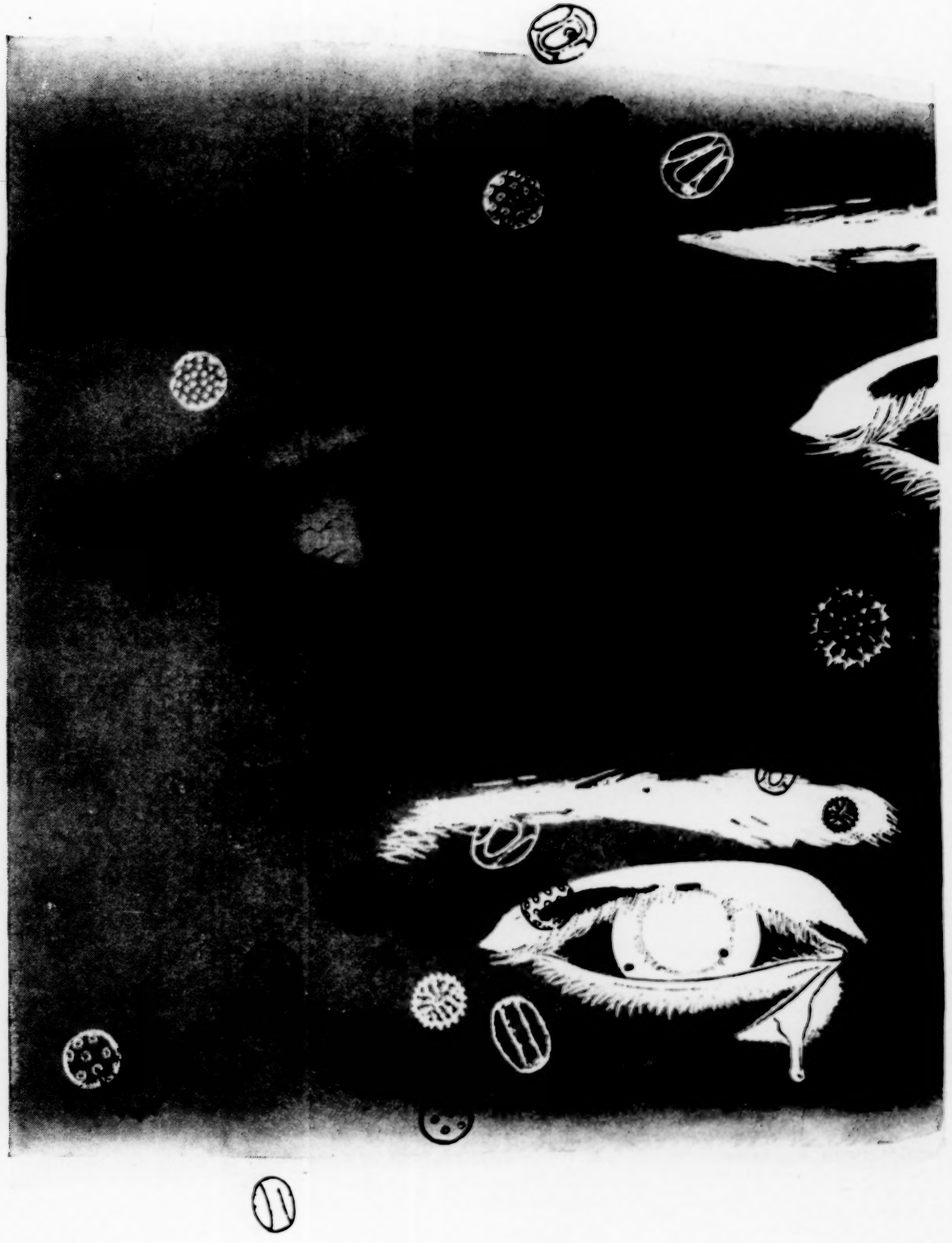

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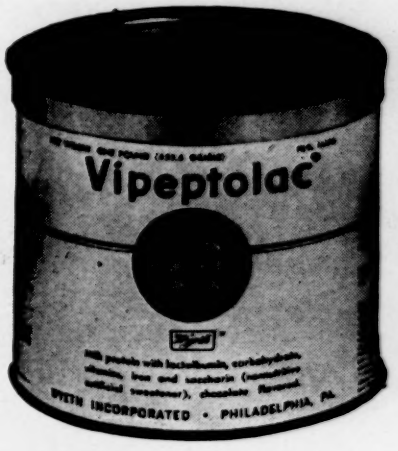

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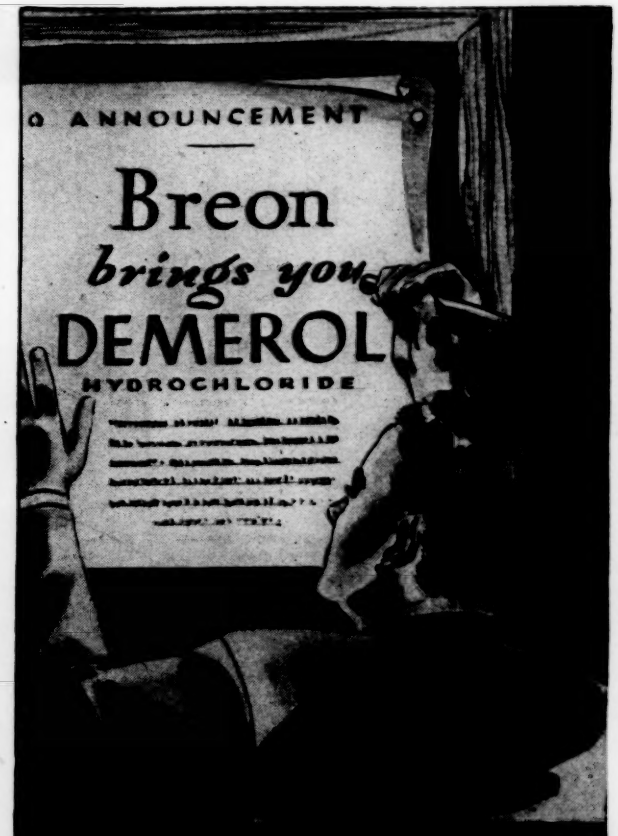

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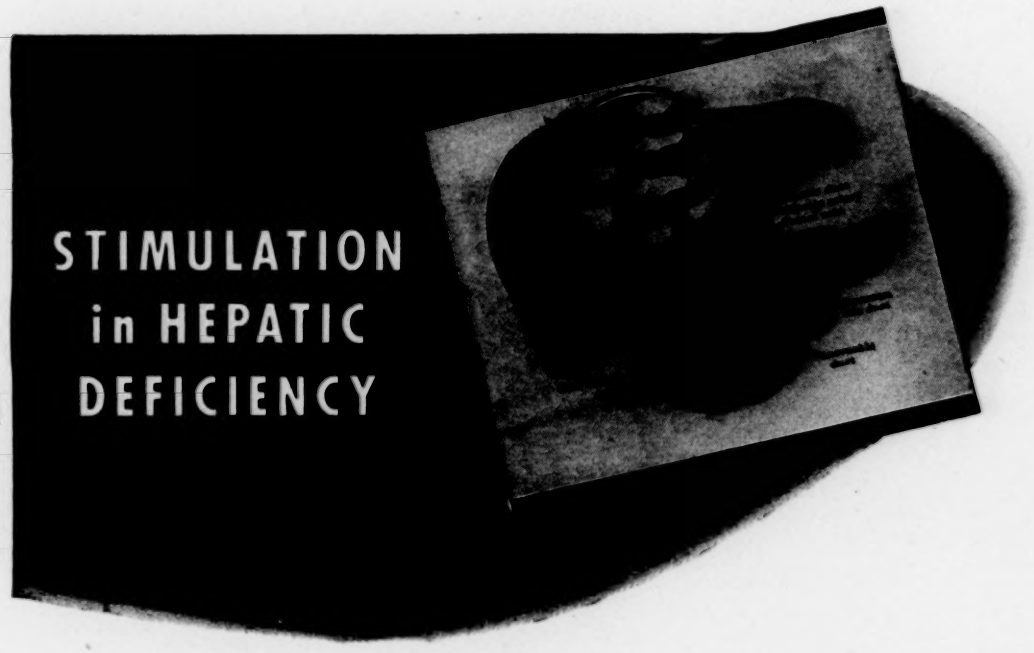

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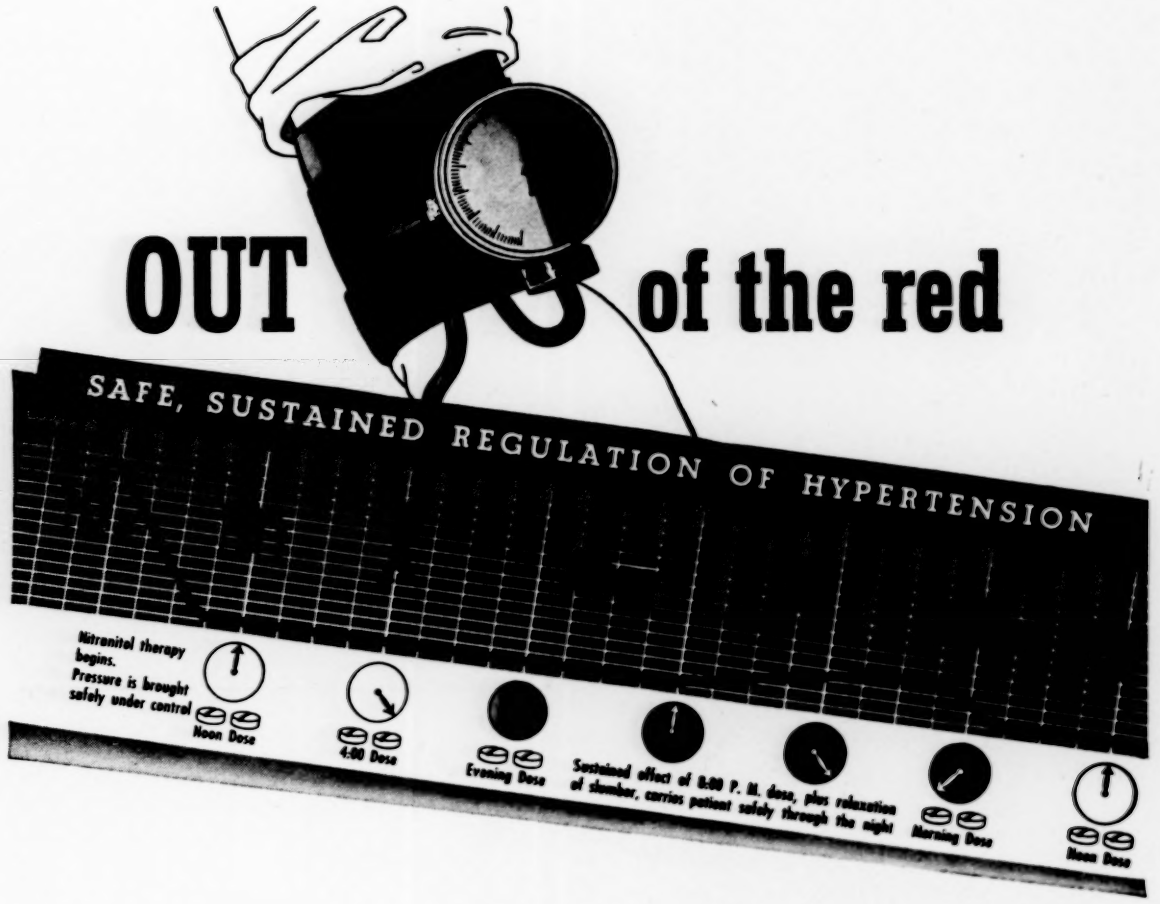

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1. Eisenstein, M. I., and Bendo, G. J.: A. J. S. 74:200
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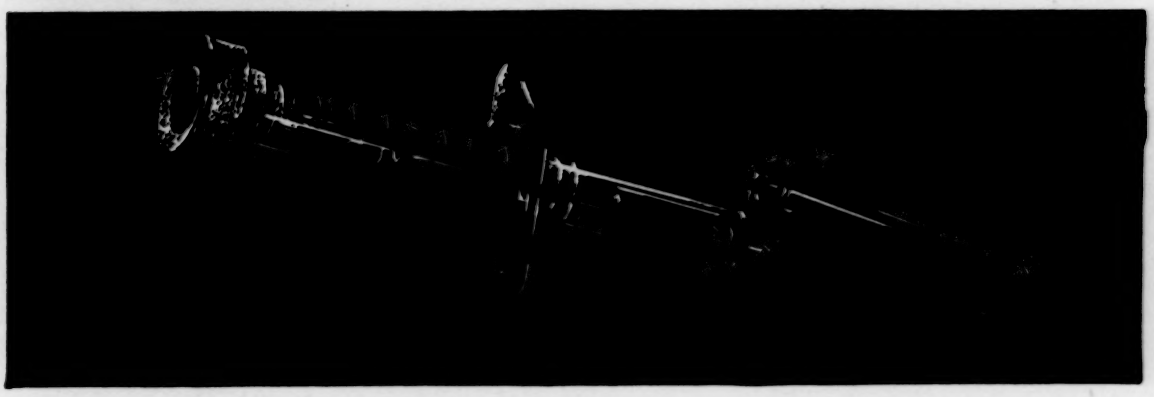

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VOL. III SEPTEMBER, 1947 No. 3

Editorial

Late Results in Peptic Ulcer

PEPTIC ulcer, whether gastric or duodenal, has a natural tendency to heal. In some instances this occurs without any medical supervision, and usually, when the lesion is of recent origin and uncomplicated, the symptoms can promptly be brought under control by the frequent feeding of a non-irritating and nutritionally adequate diet together with the avoidance of undue physical and nervous strain. Recurrence of activity, often with complications, is common, however, irrespective of the degree of gastric acidity and of whether additional therapeutic procedures, such as bed rest, antacid medication, sedation and even psychiatric measures, were originally employed. Apparently this results from some poorly understood predisposition on the part of the patient and the fact that, because of the relatively long intervals of freedom from symptoms, he tends to revert to his customary life habits.

A review of the current literature on the ultimate results in this disease is discouraging. It indicates that less than half of the roentgenologically diagnosed peptic ulcer patients are permanently cured on a medical basis. Of 216 such patients followed for ten years, Holland and Logan[1] found only 38 per cent without a recurrence and, in 1938, Crohn[2] reported only 27 per cent of his patients cured after four years. Nicol[3] had good results in only 38.5 per cent of 278 patients after two to twelve years, and some of them had symptoms when indiscreet about their diet. Raimondi and Collen[4] had an 83 per cent incidence of recurrence in patients treated for two years, and St. John and Flood[5] only 22 per cent free of recurrence after five years. Only Eustermann and Balfour[6] give more encouraging results: 65 per cent of 600 duodenal ulcer patients cured or relieved after three to five years.

In a recent report[7] on 923 patients followed from one to ten years at the University of Pennsylvania Hospital, most of them treated originally on an ambulatory basis, 31.5 per cent had come to operation within the first year of observation for a refractory status or some complication, other than malignancy, and an additional 14 per cent were still having symptoms irregularly; of the 444 patients followed for five years, 36

[1] HOLLAND, A. L. and LOGAN, V. W. Brief report of follow-up research in peptic ulcer covering 20 years. *Tr. Am. Therap. Soc.*, 41: 86, 1942.

[2] CROHN, B. B. Gastroduodenal ulcer: etiology, treatment and end results. *New England J. Med.*, 218: 128, 1938.

[3] NICOL, B. N. Peptic ulceration: results of modern treatment. *Lancet*, 1: 466, 1942.

[4] RAIMONDI, P. J. and COLLEN, M. F. Recurrent rate of symptoms in peptic ulcer patients on conservative medical treatment. *Gastroenterology*, 6: 176, 1946.

[5] ST. JOHN, F. B. and FLOOD, C. A. Study of results of medical treatment of duodenal ulcer. *Ann. Surg.*, 110: 37, 1939.

[6] EUSTERMANN, G. B. and BALFOUR, D. C. Stomach and Duodenum. Philadelphia, 1936, W. B. Saunders & Co.

[7] MILLER, T. G. Results from the treatment of peptic ulcer. *J. Michigan M. Soc.*, 46: 198, 1947.

per cent had been operated upon and another 11 per cent were medical failures; of the 166 followed for ten or more years, 45 per cent had been operated upon and an additional 10 per cent were not relieved. On the other hand, it is interesting to note that of the patients operated upon and followed for corresponding periods of time—one, five and ten or more years—the satisfactory results were about 80 per cent in each instance. Thus, although a medical regimen obviously failed in about half the cases, the total therapy, including surgery, led to symptomatic relief in approximately four of every five cases for each follow-up period. This consistent level of relief from symptoms for the varying periods of observation was accomplished, however, only by subjecting a steadily increasing percentage of the patients to surgical interference, from 31 per cent for the one-year group to 45 per cent for the ten or more year group.

In view of these results a most important aspect of the management of the peptic ulcer patient is to acquaint him at the first opportunity with the marked tendency to a recurrence of activity and to serious complications, so that he may make every reasonable effort to maintain a dietary and hygienic program designed to avoid such developments. The fact that many ulcers heal spontaneously is probably dependent on the fact that the leading symptom is that of hunger, which naturally leads to the ingestion of food substances between regular meals. Such frequent feedings, provided they are of a non-irritating nature, constitute the chief therapeutic procedure in the prevention and cure of the disease.

T. Grier Miller, M.D.

Clinical Studies

Penicillin Aerosol Therapy in Bronchiectasis, Lung Abscess and Chronic Bronchitis*

BETTINA GARTHWAITE, M.D. *and* ALVAN L. BARACH, M.D.
with the technical assistance of
EVA LEVENSON, B.A. *and* DORA RADER, PH.G., B.A., M.S.
NEW YORK, NEW YORK

To understand the rationale of antibiotic aerosol therapy in certain types of pulmonary and bronchial suppurative disease, it should be remembered that the normal bronchial tree has both ventilatory and drainage functions. The bronchi and bronchioles lengthen and widen in inspiration, and shorten and narrow in expiration. Drainage is facilitated by these rhythmic contractions, by the normal ciliary action of the epithelium of the tracheobronchial tree, and by the expulsive force of the elastic recoil of the lungs and piston-action of the diaphragm in expiration.

The anatomical changes occurring in bronchiectasis are permanent. Actual destruction of bronchial musculature and elastic tissue may occur as a result of suppuration, accompanied by dilatation of the bronchial wall, which may be cylindrical or saccular in character. The bronchial epithelium in the involved region may change from ciliated columnar to cuboidal or squamous, with loss of the protective ciliary action. The site of commonest involvement is in the peripheral bronchioles. A certain amount of fibrosis of the bronchial wall occurs in the repair process as well as in peribronchial lung parenchyma, with or without associated emphysema.

In suppuration involving the pulmonary parenchyma, excavation may occur, with varying degrees of pneumonitis surrounding the lung abscess. If the abscess heals and closes, there is a residual fibrous scar. Bronchiectasis of the segmental bronchioles may be present. Even with complete *x*-ray clearing by stereoscopic films of the chest, a residual abscess cavity, or evidence of bronchiectasis, may be demonstrated by lipiodol instillation.

In both bronchiectasis and residual lung abscess, repeated respiratory infections cause exacerbation of the original disease. Local extension of the lesion may occur, or bronchogenic dissemination to other portions of the lung. Concomitantly, pulmonary fibrosis with secondary emphysema may develop, resulting in appreciable loss of pulmonary function and further stagnation of purulent material in involved areas.

Chronic bronchitis is uncommon as a separate disease entity. It is characterized by inflammation of the bronchial mucosa with hyperemia and edema, which may result in some areas of mucosal hypertrophy and others of atrophy. The bronchial walls and peribronchial tissue usually show fibrosis. Some dilatation of the bronchi may occur.

In cases in which a diagnosis of bronchiec-

* From the Department of Medicine, College of Physicians and Surgeons, Columbia University and the Presbyterian Hospital, New York. This study was aided in part by a grant from the Josiah Macy, Jr. Foundation.

tasis, lung abscess or chronic bronchitis has been made, bronchoscopy is generally indicated to rule out obstruction in the tracheobronchial tree which would interfere with free drainage and ventilation.

The aim of medical management in these diseases is control of infection and prevention of further irreparable damage. If there is no obstruction, drainage of purulent exudates may be facilitated via the tracheobronchial tree either by postural drainage or by bronchoscopic aspiration. General hygienic measures and supportive therapy play a rôle. Use of oral sulfonamides has been disappointing on the whole except in control of some acute flare-ups when sputum cultures reveal the presence of sulfonamide-sensitive bacteria. Penicillin by intramuscular injection has been of considerable value. Surgery remains the treatment of choice in cases of bronchiectasis localized to a lobe or to lobes which may safely be extirpated. Many cases of chronic lung abscess require surgery, either drainage, lobectomy or pneumonectomy, for complete clinical cure. In considering cases of acute lung abscess and suppurative pneumonia, the advent of antibiotics has decreased the incidence of those requiring surgical intervention. Use of antibiotic therapy pre- and postoperatively has resulted in a decrease in postoperative complications and in operative mortality.

The purpose of antibiotic aerosol therapy is two-fold: first, local application of the drug to the diseased part; and second, systemic absorption of the drug via the pulmonary capillary bed.

HISTORY

The inhalation of nebulized solutions was extensively studied by Heubner (1919–1925),[1] who noted that the production of fine particles was necessary for penetration to the bronchioles and the alveoli. The beneficial clinical results of inhalation of an aerosolized solution of 1:1000 epinephrine was correlated with an observed increase in vital capacity and velocity of breathing by Lageder.[2] Although many other drugs, such as glycerin, camphor and creosote, were tried in earlier investigations, bronchodilator substances were found most useful, especially 1:100 epinephrine with the hand bulb nebulizer proposed by Graeser and Rowe.[3] Continuous nebulization with oxygen from a high pressure cylinder was employed in our clinic to nebulize 1:100 epinephrine and 1 per cent neosynephrine in the treatment of asthma and pulmonary emphysema[4,5] and later for chemotherapeutic substances, such as promine[6] and the sulfonamides.[7]

That nebulized solutions penetrated to the depths of the lungs was clearly confirmed by the careful studies of Castex, Capedehourat and Pedace[8] as well as by Krueger et al.[9] In a clinical study by Castex et al.[10] inhalation of nebulized 5 per cent aqueous sulfanilamide was shown to be followed by marked clinical improvement in cases of bronchopulmonary suppuration. Clinical improvement following inhalation of nebulized sulfathiazole was reported by Stacey[11] and others whose observations have recently been reviewed by Segal.[12] In 1944, Bryson, Sansome and Laskin[13] demonstrated that penicillin aerosol was absorbed in the lungs and excreted in the urine in substantial amounts in a normal human subject and in rabbits.

The clinical effectiveness of inhalation of penicillin aerosol by various technics in patients with bronchial asthma, bronchitis, bronchiectasis, lung abscess and pulmonary emphysema was described by Barach et al.[14,15,16] This study indicated that the predominating gram-positive organisms in the sputum culture were absent following adequate penicillin aerosol therapy and that gram-negative organisms, such as B. aerogenes, B. coli and B. pyocyaneus appeared

in the sputum culture. An effective blood level was maintained in addition to the application topically of penicillin. Since that time, favorable reports on the inhalation of penicillin aerosol have appeared, notably by Segal[17,18,19] in cases of bronchiectasis, lobar pneumonia and lung abscess; by Olsen[20,21,22] in bronchiectasis; and by Vermilye[23] in bronchial asthma and various types of sino-bronchial infection. Anderson and di St. Agnese[24] showed that children with a staphylococcus bronchitis and pneumonitis which developed in association with pancreatic disease were markedly benefited at times by inhalation of penicillin aerosol when improvement had not been obtained previously by intramuscular injection of penicillin.

Interest in the inhalation of nebulized penicillin was promptly aroused in England where Mutch and Rewell[25] and Knott and Clark[26] carried out experimental studies on the production and absorption of aerosols, and clinical studies were made by Humphrey and Joules,[27] Southwell,[28] Knott and Southwell.[29] Studies on the methods and clinical application of penicillin aerosol have been continued in our clinic, especially in the development of a method for introducing the drug into the sinuses by previous intermittent production of negative pressure in the nasal passages.[30,31,32]

METHODS

Various modifications have been made in the nebulizer apparatus as well as in technics of inhalation since the earlier methods of aerosol therapy were reported. These modifications were intended to conserve penicillin, to give the highest possible local deposition of the drug, to insure maximum absorption into the blood stream, to increase the comfort and ease of inhalation and to decrease the incidence of local penicillin reactions manifested chiefly by a sore, reddened or blackened tongue.

Substitution of a 2.5 liter latex rebreathing bag for the enlarged glass bulb gives an adequate ventilation volume with less bulky apparatus. The lips are closed around the glass mouth attachment so that expired penicillin aerosol collects in the rebreathing bag and may be re-inhaled with freshly nebulized penicillin. A Y-tube inserted in the rubber pressure tubing between the oxygen regulator and the nebulizer allows nebulization of penicillin on inspiration only, since the patient closes the open end of the Y-tube with a finger at the start of inspiration and releases it at the end of inspiration, letting oxygen escape during the expiratory phase. Holding the breath for a second or two at the end of inspiration increases local deposition of the aerosol particles.

Oxygen is generally employed as the gas to nebulize the solution. Air from a pressure compressor may be used, or air supplied by means of an ordinary automobile tire foot-pump.[33] The latter has the advantage of being inexpensive and dispenses with the need for oxygen equipment in the home. If the patient is bedridden or too ill to work the pump himself, it can be operated by another person.

We have found the Vaponefrin nebulizer the most satisfactory of the various commercial nebulizers in regard to particle size of the aerosol. Investigators[34] reported that the majority of the particles are less than 1 micron in diameter. From studies under progress at the present time[35] a wider variation than was previously accepted has been found in particle size of aerosols produced by such nebulizers. Attempts are being made to determine the ideal diameter of particles for use as therapeutic aerosols, and thereafter to construct a nebulizer to produce as efficiently as possible an aerosol of such uniform particle size. Larger sized particles, such as those produced by some commercial nebulizers, tend to lodge on the

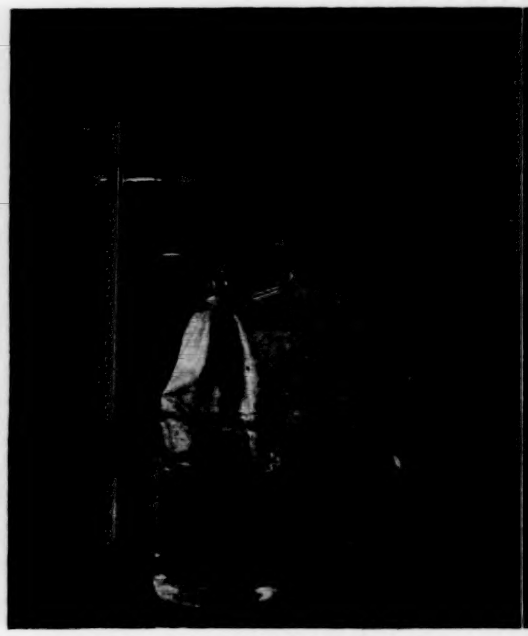

FIG. 1. Mouth inhalation apparatus with Vaponefrin nebulizer, curved glass baffle and mouth attachment with rebreathing bag immersed in hot water.

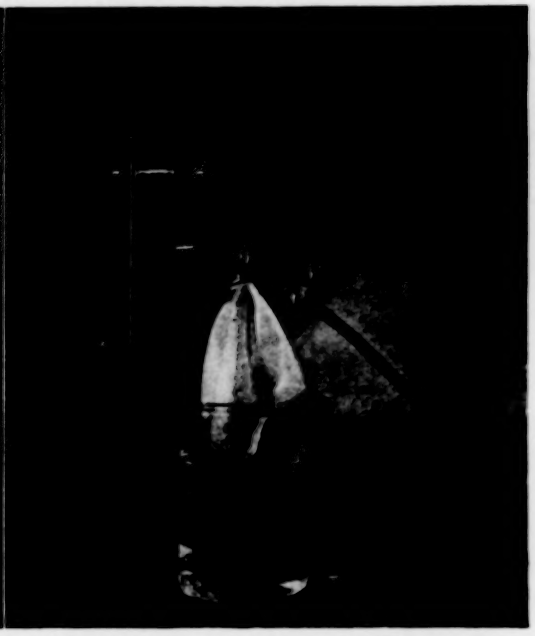

FIG. 2. Mouth inhalation apparatus with "small-particle-size" nebulizer connected to mouth attachment and rebreathing bag immersed in hot water.

tongue, pharynx and larynx and do not reach the bronchi, bronchioles or alveoli. Particles much smaller in size tend to be exhaled instead of deposited on the bronchopulmonary surface. By incorporation of a glass baffle between the Vaponefrin nebulizer and the mouth rebreathing attachment, the larger particles are baffled out and drain back into the nebulizer where the solution is renebulized. (Fig. 1.) A special nebulizer has been constructed which gives comparable results by producing an aerosol of finer particle size, with fair uniformity of particles and which eliminates the need for an additional glass baffle in the apparatus. (Fig. 2.)

Attachment of a metal water bottle to the oxygen regulator, although not an essential item, conserves penicillin by diminishing evaporation in the nebulizer. The oxygen flow employed varies from 8 to 12 liters per minute.

It has been found that comfort of inhalation is enhanced by providing a warm, humidified aerosol. This is accomplished by placing a glassful of very hot water in the rebreathing bag immersed in a container of hot water. This modification also has decreased the incidence of local sensitivity reactions by surrounding the aerosol particles with water vapor. Patients who have previously shown a sore tongue reaction to penicillin aerosol are advised to rinse the mouth and gargle with tap water or warm saline following each treatment.*

Originally it was found that the calcium salt of penicillin was less irritating for aerosol use than the sodium salt. Since crystalline preparations have become available, they are the preparation of choice, in the form either of the crystalline sodium or

* More effective prevention of sore tongue is obtained by sipping water and rinsing the throat before and during inhalation of penicillin aerosol. Moistening the back of the throat by spraying with tap water, using a conventional atomizer, is probably the simplest and best method of avoiding irritation of the throat. This should be done before and during inhalation. The large particles that lodge on the pharynx are then taken up into solution on the moistened surface and subsequently absorbed. If this procedure is carried out, it is unnecessary to use hot water in the rebreathing bag.

potassium salt. It should be kept in mind, however, that this material, although the purest available, still contains some impurities, and some instances of sensitivity have been encountered even with its use.

The concentration of penicillin generally employed by us has been 50,000 units dissolved in 1 cc. of physiological saline. This gives a slightly hypertonic solution, whereas distilled water as the diluent gives a hypotonic solution. To obtain an isotonic solution using crystalline sodium penicillin, Wilson[35] found that 0.35 per cent saline would be required.*

The total daily dosage of penicillin aerosol recommended in treatment of bronchiectasis, lung abscess or chronic bronchitis varies between 150,000 and 500,000 units, generally divided into three to five inhalations, with a concentration of 50,000 units per cc. In a few cases, 1,000,000 units daily have been nebulized. At least one, and preferably two rinses of 0.5 cc. each of physiological saline are added to the nebulizer at the end of each treatment and inhaled to avoid waste of the drug from concentrated residue in the nebulizer. The time required for such a treatment, using the mouth inhalation apparatus, averages thirty minutes with an oxygen flow of 10 liters per minute.

In the treatment of patients too ill to use the standard mouth inhalation apparatus, in young children, and in most cases complicated by severe pulmonary emphysema, aerosols may be administered by a nebulizer attached to an oro-nasal mask (with the inspiratory disc removed) connected directly by pressure tubing to the oxygen regulator without use of the concentration meter. (Fig. 3.) Whenever the inspiratory disc is removed the oxygen flow should be set at 8 liters per minute or higher to insure washing out of accumulated carbon dioxide from the rebreathing bag.

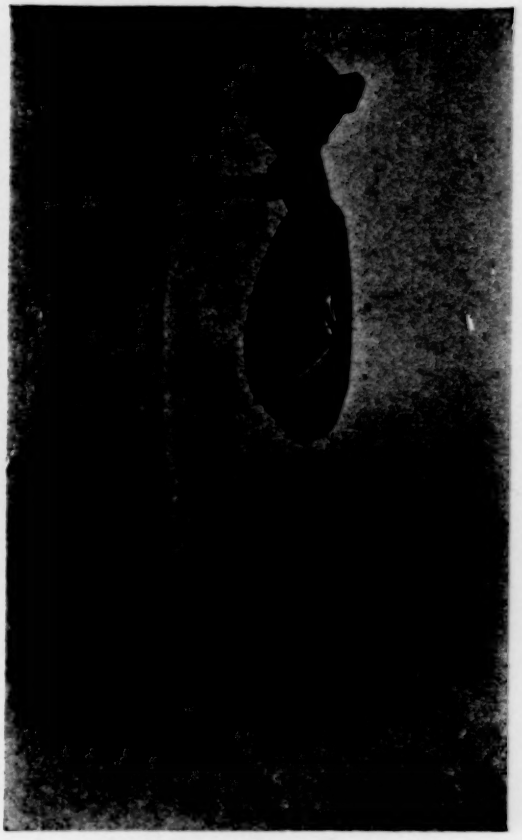

FIG. 3. Mask-nebulizer apparatus.

More recently we have become interested in methods of more continuous administration of penicillin aerosol. This may be accomplished by using the mask-nebulizer apparatus with a needle inserted through the cork of the carburetor opening in the nebulizer. The needle is then connected by infusion tubing to a large syringe or flask containing penicillin in a concentration of 5,000 to 10,000 units per cc. of saline. By use of a screw clamp on the infusion tubing, the rate of drip and consequent nebulization of solution is controlled.

A more comfortable method of continu-

* An aerosol tablet is now employed which eliminates the need for a hypodermic syringe and needle to make the solution used in nebulized penicillin therapy. The tablet contains crystalline penicillin, 50,000 units, and is inserted directly into the nebulizer; 8 to 15 minim drops of distilled or boiled water or saline are then added resulting in almost immediate solution of the crystalline penicillin tablet which is then nebulized. The crystalline penicillin tablets which we have employed were provided us by the Premo Pharmaceutical Laboratories, Inc., Commercial Solvents Corp. and the Bristol Laboratories.

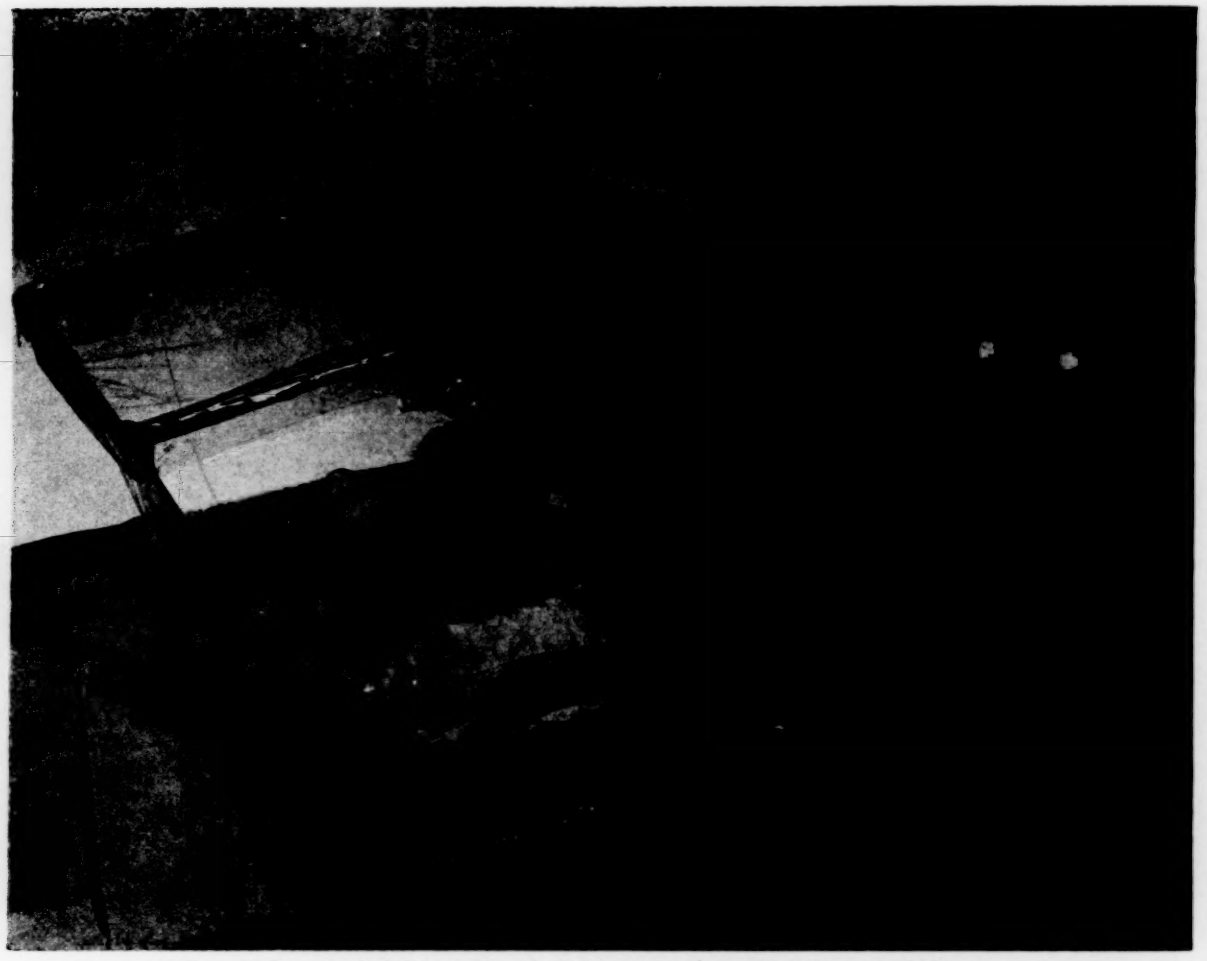

FIG. 4. Oxygen head tent for administration of continuous aerosol therapy.

ous aerosol administration is obtained by use of a clearlite oxygen head tent,[36] inside which the nebulizer is set in position so that a dense aerosol is directed towards the patient's nose and mouth. (Fig. 4.) The connection from the carburetor opening to the infusion flask is the same as for the mask-nebulizer apparatus. In the latter, 95 per cent oxygen is employed, whereas in the head tent technic an oxygen concentration of 50 to 60 per cent is obtained. By adjusting the concentration of penicillin and the rate of flow, this technic enables the patient comfortably to inhale penicillin aerosol for three to four hours at a time two to three times daily, or even continuously through the twenty-four-hour period, with only brief interruptions at meal times. The total daily dosage generally varies from 500,000 to 1,000,000 units.

Efficient treatment by aerosol therapy of the bronchopulmonary diseases under consideration necessitates local deposition of the aerosol, which can be obtained only if the bronchial passageway remains open. Therefore, if much bronchospasm or congestion of the bronchial mucosa exists it is necessary to have the patient inhale a nebulized solution of Vaponefrin and 1 per cent neosynephrine prior to each inhalation of the antibiotic substance. Substitution of helium-oxygen mixtures may be employed in cases in which it is believed that the lighter gas will penetrate into diseased areas not accessible to oxygen.

RESULTS

The results of blood level determinations in patients given test inhalations of 50,000 units of penicillin dissolved in 1 cc. normal saline are shown in Table 1.* Two or three rinses of 0.5 cc. normal saline were added to the nebulizer at the end of each treatment to allow inhalation of most of the penicillin remaining in the nebulizer. The time was measured from the start of inhalation through the end of the last rinse. The mouth inhalation apparatus was used in all these tests. Since no appreciable difference in blood levels was noted in attempting to compare the Vaponefrin nebulizer plus the glass baffle attachment with the "small particle size" nebulizer, the particular type nebulizer used has not been indicated in Table 1. However, when the same patient was tested by the various methods listed, the same apparatus was used in each test. It can be seen that there is very little difference in the blood levels obtained by these various methods.

TABLE 1

BLOOD LEVEL DETERMINATIONS AFTER INHALATION OF 50,000 UNITS PENICILLIN

Method of Inhalation	No. of Tests	Penicillin	Duration of Inhalation (Minutes)	Blood Levels (U/cc)		
				½ Hour	1 Hour	2 Hours
Cold dry aerosol	81	Calcium	35 (25–55)	0.10 (0.0–0.2)	0.07 (0.0–0.2)	0.03 (0.0–0.05)
Cold dry aerosol and water bottle	10	Calcium	60 (45–105)	0.07 (0.01–0.2)	0.13 (0.03–0.4)	0.08 (±–0.2)
Warm humidified aerosol	17	Calcium	30 (20–70)	0.09 (0.0–0.2)	0.09 (±–0.2)	0.04 (0.0–0.1)
Warm humidified aerosol and water bottle	20	Calcium	55 (40–90)	0.12 (0.05–0.2)	0.13 (0.05–0.2)	0.07 (0.01–0.2)
Cold dry aerosol	12	Sodium, crystalline	25 (10–40)	0.13 (0.0–0.4)	0.12 (0.05–0.2)	0.06 (±–0.2)
Warm humidified aerosol	14	Sodium, crystalline	30 (25–50)	0.08 (0.05–0.4)	0.16 (0.05–0.4)	0.10 (±–0.4)

However, use of the water bottle increases the time required to complete the inhalation, thereby delaying the peak blood level reached and prolonging the blood level. It prevents too high concentration of penicillin in the nebulizer towards the end of inhalation by decreasing evaporation. This is important in patients prone to develop sore tongue reactions. We have found that the concentration of penicillin remaining in the nebulizer towards the end of an inhalation is approximately double the original concentration, hence the importance of rinses of the nebulizer at the end of each inhalation, even if the water bottle is used.

From Table 1 there appears to be no increase in blood level when the warm humidified aerosol method is compared with the cold dry aerosol method, except in the tests in which crystalline sodium penicillin aerosol was used. In six patients tested with both calcium penicillin and crystalline sodium penicillin with the cold dry and warm humidified methods, there was only a slight increase in blood levels with the warm humidified method, the time required for inhalation being essentially equal. However, in identical experiments using radioactive sodium aerosol, Talbot et al.[37] found a larger amount of the aerosol retained in the body, both locally and systemically, when the warm humidified

* Blood level determinations by the Hobby dilution method.

method was employed. In regard to the patient's comfort, inhalation of a warm humidified aerosol is preferred. It also has lessened the incidence of sore tongue reactions to penicillin.

The higher blood levels obtained with the crystalline penicillin salt are attributable as much to the lower residue remaining in the nebulizer after inhalation as to higher potency of the material. Penicillin used for test inhalations was dissolved on the day of use. Its potency was checked whenever there was any doubt. Some vials of crystalline penicillin contained more than the labeled number of units. Once the crystalline salt is dissolved it retains its potency when kept in the refrigerator for one week, but loses most of its potency in forty-eight hours at room temperature.

TABLE II
RESIDUES IN APPARATUS AFTER INHALATION OF 50,000 UNITS CALCIUM PENICILLIN

No. of Tests	Type of Nebulizer	Glass Baffle Attachment	Rebreathing Bag and Mouthpiece Attachment
30	Vaponefrin nebulizer 6,000 (2,500–10,000)	1,500 (1,000–2,000)	2,500 (500–8,000)
32	SPS nebulizer with fused mouthpiece 8,000 (5,000–20,000)	.....	Rebreathing bag 2,000 (500–4,000)

Penicillin assays of the residues remaining in various parts of the mouth inhalation apparatus after inhalation of 50,000 units calcium penicillin in 1 cc. normal saline, followed by two to three rinses of 0.5 cc. saline are shown in Table II. No significant difference was noted after various methods of inhalation, so that tabulations of methods as in Table I was not indicated. The difference between individual nebulizers in the numbered series seemed to be more important, especially in regard to the closeness of contact between the vertical capillary tube and the bottom of the nebulizer, as well as to how fine and uniform a mist the nebulizer produced when judged by nebulization of methylene blue against a piece of blotting paper. It is seen from Table II that the residue of calcium penicillin in the apparatus averages 20 per cent of the original dose given. It is generally 5 to 10 per cent with crystalline penicillin salts.

TABLE III
RINSING EXPERIMENT—PENICILLIN RESIDUE IN VAPONEFRIN NEBULIZER

	No. of Rinses	Time (Min.)	Residue (Units/Cc.)
Without Water Bottle			
Calcium penicillin.....	0	5:40	20,000
	1	8:37	20,000
	2	10:32	10,000
	3	13:18	2,000
Crystalline sodium penicillin			
	0	5:41	16,000
	1	8:30	5,000
	2	12:00	4,000
	3	14:30	1,250
With Water Bottle			
Calcium penicillin.....	0	6:45	10,000
	1	9.43	5,000
	2	14:17	1,250
	3	16:00	1,250
Crystalline sodium penicillin			
	0	6:45	10,000
	1	11:04	2,500
	2	14:57	2,000
	3	18:12	500

Table III shows the results of a controlled rinsing experiment, using the same Vaponefrin nebulizer to nebulize 50,000 units penicillin dissolved in 1 cc. normal saline at an oxygen flow of 10 liters per minute, varying the number of rinses of 0.5 cc. saline each, to compare residues with or without a water bottle connected to the regulator, and to compare residues when calcium penicillin or crystalline sodium penicillin is used. It can be seen that the use of the water bottle decreases the residue more appreciably when the calcium salt is employed than when the crystalline material is used. Time required for nebulization is increased by incorporation of a water bottle. Residues are

lower when the purer crystalline material is nebulized. For practical purposes, the results indicate that one rinse is sufficient if the water bottle is used, but otherwise at least two rinses should be used. Also an additional rinse should be used if crystalline penicillin is not available.

Blood level determinations following inhalation of penicillin aerosol using the mask nebulizer apparatus result in lower values than with the standard apparatus since the expired gas carries some penicillin aerosol with it to the outside air through the expiratory flutter valve. To obtain a blood level of 0.1 to 0.2 units per cc. the dosage should usually be 100,000 units penicillin in 2 to 4 cc. normal saline when the mask is used, followed by a 1 cc. rinse. Inhalations may be given four to five times daily.

With the continuous drip method, either attached to the mask or in the head tent, using concentrations of 5,000 to 10,000 units penicillin per cc. normal saline, blood levels averaging 0.05 to 0.1 unit per cc. are obtained for several hours with the interrupted type of treatment, using a total dosage of 100,000 to 300,000 units twice daily. With continuous slow nebulization of 1,000,000 units (concentration 10,000 units per cc. normal saline) over a twenty-four-hour period in the head tent, blood levels of 0.01 to 0.03 unit per cc. constantly have been found.

Recently a number of patients have been treated with penicillin aerosol using a foot-pump as a source of power for nebulization, instead of oxygen. This method[33] is economical, requires approximately the same length of time for nebulization and results in average penicillin blood levels of 0.1 to 0.2 unit per cc. for two hours after the start of test inhalations of 50,000 units followed by two saline rinses of 0.5 cc. each.

Use of a hypertonic 3 per cent saline solution as diluent for penicillin aerosol is now being investigated and the few preliminary results show a tendency toward higher blood levels and possibly a more effective local deposition of the aerosol particles. Further studies are under progress at the present time, including a preliminary drying of the hypertonic aerosol particles by steam to decrease the particle size as they enter the upper respiratory tract, whereafter the particles become surrounded by water vapor. This results in an increase in size and weight of the particles as they reach the bronchioles and alveoli, which contributes to local deposition.[35]

Our experience with diluents other than saline or distilled water for use in penicillin aerosol therapy has led to the conclusion that such substances as 1 per cent neosynephrine or Vaponefrin, 5 per cent glycerol, 5 per cent to 50 per cent propylene glycol or triethylene glycol and 0.1 to 0.2 per cent aerosol O.T. are not as efficacious. Use of the vasoconstrictor drugs results uniformly in lower blood levels and the absorption curve is not prolonged, although the peak of the curve may be delayed to one or one and a half hours after the start of inhalation. Various diluents which give a more stable mist have the disadvantage of increased viscosity in higher concentrations, which slows nebulization considerably and frequently plugs the nebulizer toward the end of the treatment. With the use of 5 per cent triethylene glycol, penicillin blood levels are about 30 per cent lower than when penicillin is dissolved in normal saline in comparable test inhalations on the same patients. In a small series of these patients, however, inhalation of radioactive sodium dissolved in 5 per cent triethylene glycol resulted both in greater local deposition of the aerosol and in increased absorption.[37]

A few patients had blood level determinations made after intramuscular injections of penicillin for comparison with levels obtained after inhalation of penicillin aerosol. In general, two to three times as much

penicillin must be given by inhalation to insure as high a level of penicillin in the blood stream, although this varies to a considerable degree with the extent of the bronchopulmonary disease. Contrary to Segal's report,[17] we find that normal individuals obtain higher blood levels after inhalation of penicillin than patients with chronic bronchopulmonary disease. The greater the involvement the lower the absorption, as a rule. In regard to lobar pneumonia it should be remembered that once consolidation is established, the benefit derived from penicillin aerosol is exerted through absorption of the drug into the blood stream in portions of uninvolved lung. We have obtained striking clinical improvement in a few patients with advanced bronchiectasis, pulmonary fibrosis and emphysema, who never had an effective penicillin blood level demonstrated after test inhalations. Furthermore, some patients failed to improve after massive doses of intramuscular penicillin, but subsequently improved on penicillin aerosol alone, although much lower blood levels were obtained, indicating the necessity for a therapeutically effective local concentration of penicillin. Apparently in some cases of bronchopulmonary suppuration in which bacteria grow on surfaces covered by fibrinopurulent exudate the capillary blood supply may be inadequate to insure a local therapeutic penicillin level, whereas inhalation of the drug insures adequate local concentration if the airway remains patent.

Although Knott and Southwell[29] reported a higher concentration of penicillin in arterial blood than in venous blood during penicillin aerosol administration, we failed to confirm these results, finding identical levels in a few instances in which simultaneous arterial and venous blood specimens were obtained. In their animal experiments these authors demonstrated a considerable concentration of penicillin in lung tissue. They suggested the use of penicillin aerosol in an oxygen tent and reported results of the degree of penicillin absorption in nine children with minor respiratory infections. Clinical results in serious respiratory infections were not evaluated although early results looked promising.

Recently sputum specimens have been tested for assay of penicillin at various times after inhalation of penicillin aerosol and also after intramuscular administration of penicillin. Results thus far show that after single inhalation of 50,000 units penicillin, the concentration of penicillin sputum produced during the first one to four hours varies between 10 and 1,280 units per cc., with an average of 461 units per cc. With inhalation of 50,000 units penicillin dissolved in 5 cc. normal saline using the mask-nebulizer apparatus, one patient has shown a level of 640 units per cc. sputum for three hours after the time of administration of penicillin. Five patients failed to show demonstrable penicillin sputum levels after a single intramuscular injection. Twenty patients tested have shown no penicillin present in twenty-four-hour sputum samples while receiving 40,000 to 100,000 units of penicillin every 3 hours by intramuscular injection. In assays of total amount of sputum collected over a twenty-four-hour period from patients receiving 50,000 to 100,000 units penicillin aerosol four times daily, with the mouth inhalation apparatus, concentrations of 20 to 400 units per cc. sputum have been obtained. With the same dosage by mask nebulizer technic, penicillin sputum levels range from 10 to 245 units per cc. Two twenty-four-hour penicillin sputum assays in a patient receiving 900,000 units by slow continuous aerosol drip in an oxygen head tent over a twenty-four-hour period showed 1,600 and 640 units per cc. sputum, but two other tests were negative. The sputum jars for collections over more

TABLE IV

CLINICAL RESULTS OF PENICILLIN THERAPY IN BRONCHIECTASIS

Case No.	Age	Sex	Additional Diagnosis	Course	Clinical Improvement Due to Penicillin	Administration of Penicillin		
						Route	Total Dosage	Duration (Weeks)
1	29	F	Pulmonary emphysema	1	slight	Inhalation	5,280,000	5
2	57	M	Bronchial asthma Pulmonary emphysema Chronic sinusitis	1	marked	Inhalation	1,400,000	1
				2	none	Inhalation	2,400,000	3
				3	slight	Inhalation Intramuscular	1,728,000 1,030,000	2.7
				4	slight	Inhalation Intramuscular	4,350,000 3,180,000	5 1.7
3	62	M	Pulmonary emphysema	1	moderate	Inhalation	1,040,000	1.5
4	59	M	Pulmonary fibrosis	1	moderate	Intramuscular Inhalation	1,200,000 700,000	1 0.7
				2	moderate	Inhalation	1,900,000	2.7
5	56	F	Pulmonary emphysema Pulmonary fibrosis	1	marked	Inhalation	950,000	0.7
				2	moderate	Inhalation Intramuscular	2,300,000 600,000	2 1
				3	slight	Inhalation Subcutaneous	2,440,000 1,180,000	2 0.5
				4	slight	Oral	60,000,000	13
				5	none	Inhalation	500,000	0.5
6	21	M	Pulmonary emphysema Bronchial asthma	1	moderate	Inhalation Intramuscular	600,000 700,000	0.5 1
				2	none	Inhalation	1,800,000	1.7
				3	slight	Inhalation Intramuscular	1,000,000 1,080,000	1
				4	none	Oral	8,000,000	2
				5	marked	Inhalation	50,000 units 4 × daily	18 months
7	27	M	Bronchial asthma Chronic sinusitis	1	marked	Inhalation Intramuscular	8,500,000 1,215,000	6 3
8	47	M	Bronchial asthma Pulmonary emphysema Pulmonary fibrosis Rheumatoid arthritis	1	none	Inhalation Intramuscular	540,000 1,155,000	0.7 1.5
				2	none	Inhalation Oral Intramuscular	3,250,000 3,300,000 7,650,000	8
9	69	M	Pulmonary emphysema Chronic sinusitis	1	moderate	Inhalation	1,300,000	1
10	60	M	Bronchial asthma Pulmonary emphysema	1	moderate	Inhalation Intramuscular	1,300,000 1,000,000	1
				2	slight	Inhalation	2,000,000	2
				3	slight	Inhalation	1,000,000 (crystalline sodium penicillin)	1.5
11	18	M	Chronic sinusitis	1	moderate	Inhalation Intramuscular	2,800,000 4,350,000	1.5
				2	marked	Inhalation	3,525,000	2.3
				3	marked	Inhalation	30,000,000	30
				4	moderate	Inhalation Inhalation (Nasal Suction)	2,500,000 600,000	1.5 0.5
12	52	M	None	1	slight	Intramuscular Inhalation	1,475,000 1,500,000	1
13	67	F	Pulmonary emphysema	1	marked	Intramuscular Inhalation	1,700,000 1,750,000	1.5

TABLE IV (*Continued*)

Case No.	Age	Sex	Additional Diagnosis	Course	Clinical Improvement Due to Penicillin	Administration of Penicillin		
						Route	Total Dosage	Duration (Weeks)
14	18	F	None	1	moderate	Inhalation	6,750,000	3
						Intramuscular	1,600,000	3
15	55	F	Chronic sinusitis	1	moderate	Oral	6,000,000	1.5
				2	moderate	Oral	7,000,000	1.5
				3	slight	Inhalation (Nasal Suction)	500,000	2
16	60	M	Pulmonary emphysema	1	none	Intramuscular	1,450,000	2
			Pulmonary fibrosis			Inhalation	960,000	1
17	59	F	Chronic sinusitis	1	slight	Intramuscular	480,000	0.7
			Rheumatoid arthritis			Inhalation	800,000	
18	54	F	Pulmonary emphysema	1	none	Inhalation	2,650,000	2
			Pulmonary fibrosis					
19	46	M	None	1	slight	Inhalation	3,230,000	2.5
						Intramuscular	1,800,000	
20	21	F	Pulmonary emphysema	1	slight	Inhalation	4,000,000	4
			Nutritional edema					
21	71	M	Pulmonary emphysema	1	marked	Inhalation	1,250,000	0.8
			Pulmonary fibrosis					
				2	marked	Inhalation	900,000	28
22	21	M	None	1	moderate	Intramuscular	1,120,000	1
						Inhalation	2,800,000	2
23	9	F	Pulmonary emphysema	1	moderate	Inhalation	1,680,000	2
			Chronic sinusitis					
				2	moderate	Inhalation	3,250,000	2.5
						Inhalation (Nasal Suction)	3,750,000	3.5
				3	moderate	Inhalation	30,000,000	20
24	48	M	Bronchogenic carcinoma	1	marked	Inhalation	1,400,000	1
						Intramuscular	2,600,000	2
25	27	M	Chronic sinusitis	1	moderate	Inhalation	3,600,000	2.5
						Intramuscular	700,000	1
26	16	M	Chronic sinusitis	1	moderate	Inhalation (Nasal Suction)	3,000,000	2
				2	moderate	Inhalation	4,500,000	4.5
27	24	F	Chronic sinusitis	1	marked	Inhalation	5,250,000	5
28	28	F	Chronic sinusitis	1	marked	Inhalation	9,000,000	9
						Intramuscular	1,120,000	1
29	25	F	Pulmonary emphysema	1	slight	Inhalation	3,000,000	3
			Chronic sinusitis					
30	27	M	Pulmonary emphysema	1	moderate	Inhalation	22,500,000	20
			Chronic sinusitis					
31	16	F	None	1	marked	Inhalation	18,000,000	17
				2	recovery (due to surgery)	Intramuscular	360,000 pre-op.	0.3
						Intramuscular	2,520,000 postop.	1.6
32	33	F	None	1	marked	Inhalation	12,000,000	9
33	16	M	Suppurative broncho-pneumonia	1	slight to moderate	Transmuscular	49,000,000	3.5
			Chronic sinusitis					
				2	marked	Inhalation	7,000,000	1
						Inhalation	7,200,000	2.5
34	57	M	Pulmonary emphysema	1	moderate	Inhalation	3,500,000	3
35	70	M	Pulmonary emphysema	1	moderate	Inhalation	4,500,000	5
			Cardiac insufficiency (ASHD and ? cor pulmonale)					

TABLE V

EFFECT OF PENICILLIN THERAPY ON SPUTUM CULTURES IN BRONCHIECTASIS

Case No.	Course	Sputum Cultures		Remarks
		Before Treatment	After Treatment	
1	1	Hemolytic Strep. Non-hemolytic Strep. Staph. aureus	None	Decrease in cough and expectoration. No change in chest x-rays before and after treatment
2	1	Strep. viridans	B. pyocyaneus	Marked improvement in all symptoms, sustained only one month
	2	Strep. viridans	B. pyocyaneus B. aerogenes	Asthma became intractable
	3	B. pyocyaneus	B. pyocyaneus	Subsequent courses of penicillin gave slight and temporary benefit
	4	Hemolytic B. pyocyaneus	Hemolytic B. pyocyaneus	
3	1	Strep. viridans	B. aerogenes	Decrease in cough and expectoration and dyspnea, but improvement sustained only one month
4	1	Hemolytic Strep. Strep. viridans Staph. albus	B. aerogenes	No improvement on course of 1 week I.M. penicillin, but temporary improvement with both courses of aerosol. Treatment discontinued twice because of urticaria and sore, reddened tongue and throat
	2	None	None	
5	1	Strep. viridans	Strep. viridans	Increased cough on sodium penicillin aerosol
	2	Strep. viridans	Strep. viridans	Pruritus on intramuscular penicillin.
	3	No growth	B. aerogenes	Local soreness and blisters at S.C. injection sites
	4	None	None	Prolonged course on oral penicillin at home with slight benefit
	5	Strep. viridans	B. coli	Bronchial relaxation program most helpful
6	1	Strep. viridans	None	Benefit not sustained
	2	Strep. viridans	B. aerogenes	Sore, reddened throat on sodium salt, increased asthma and pulmonary edema
	3	None	B. aerogenes	Edema of feet and ankles; urticaria
	4	Strep. viridans	B. aerogenes	No change in symptoms
	5	Strep. viridans Staph. aureus	B. coli Occasional Strep. viridans	Remarkable and sustained improvement throughout period of continuous therapy. No other medication necessary except for occasional Vaponefrin or oral aminophyllin
7	1	Strep. viridans Staph. aureus	B. aerogenes	Reddened sore throat and irritative cough on sodium salt. Improvement in all symptoms except those due to sinusitis
8	1	Strep. viridans	B. aerogenes B. coli	Increased cough on sodium salt. Soreness at injection sites. Intractable asthma unchanged. No change in symptoms
	2	Strep. viridans	B. aerogenes	
9	1	Pneumococcus, type 12	B. coli	Decrease in cough and expectoration
10	1	Strep. viridans	B. coli	Developed fever, urticaria, aggravation of asthma and sore, reddened tongue
	2	Strep. viridans	B. aerogenes	Sore reddened tongue, aggravation of asthma
	3	Non-hemolytic Strep.	B. coli	Decrease in cough and expectoration but increase in dyspnea and wheezing
11	1	Staph. albus	B. aerogenes	Penicillin stopped because of urticaria. Improvement sustained 5 months
	2	Hemolytic Strep.	B. aerogenes	Had course of 1,200,000 units streptomycin aerosol prior to penicillin therapy
	3	Gram-pos cocci Gram-pos. and neg. bacilli	Gram-neg. bacilli	Improvement sustained by continuous penicillin aerosol treatment at home during winter and spring

TABLE V (*Continued*)

Case No.	Course	Sputum Cultures		Remarks
		Before Treatment	After Treatment	
	4	Staph. albus Strep. viridans	B. aerogenes	0.25% p-chlorophenol used as diluent for penicillin, but provoked irritative cough during first week. Sustained improvement less marked than previously
12	1	Strep. viridans	None	Urticaria necessitated stopping therapy
13	1	None	B. coli† B. aerogenes†	Cough became non-productive
14	1	H. influenzae	B. aerogenes Strep. viridans	Aerosol pre-operatively. I.M. penicillin following left lower lobe lobectomy. Febrile postoperative course with repeated thoracenteses (fluid sterile). Follow-up unremarkable
15	1	Staph. albus Strep. viridans	None	Symptomatic improvement
	2	H. hemolyticus H. influenzae	B. coli B. aerogenes H. influenzae	Temporary improvement. Rales less numerous
	3	Staph. albus Strep. viridans	None	Symptomatic improvement without change in sinus *x*-rays
16	1	None	None	Urticaria on I.M. penicillin. Bronchial relaxation program helpful
17	1	Strep. viridans	None	Urticaria
18	1	None	B. coli B. aerogenes	Urticaria
	2	Strep. viridans	None	Urticaria
19	1	None	None	Decrease in cough and expectoration. Improvement not sustained
20	1	Hemolytic Staph. aureus Staph. albus	Strep. viridans	Striking improvement attributed chiefly to general supportive measures
21	1	Strep. viridans	B. coli Few Staph. aureus	Marked decrease in cough and expectoration; improvement in general well-being with progressive weight gain. Benefit sustained by weekly inhalations without additional medication for past 6 months
	2	D. pneumoniae	B. coli	
22	1	Strep. viridans	B. coli	Cough became non-productive. *X*-ray clearing of bronchopneumonia
23	1	None	None	
	2	Pneumococcus, type 6	Strep. viridans Non-hemolytic Strep. H. influenzae	Had left pneumonectomy several years ago for bronchiectasis. Advanced bronchiectasis in remaining lung. Penicillin aerosol, with continuous treatment at home, keeps patient ambulatory. Sinus and chest *x*-rays unchanged. Now on sodium sulfacetimide aerosol
		D. pneumoniae	H. influenzae B. coli	
24	1	Staph. aureus Non-hemolytic Strep.	None	Marked symptomatic improvement on aerosol therapy pre-operatively. Uneventful postoperative course (pneumonectomy) on I.M. penicillin
25	1	D. pneumoniae Strep. viridans	B. aerogenes	Decrease in cough and expectoration, sputum losing foul odor
26	1	Hemolytic Strep.*	B. coli†	Case of minimal bronchiectasis, with involvement of both lower lobes, became asymptomatic. Later non-productive cough recurred, but less severe
	2	None	Strep. viridans	
27	1	Non-hemolytic Strep. Staph. aureus	B. coli	Minimal bronchiectasis. All symptoms disappeared on penicillin aerosol. Benefit sustained 6 months

TABLE V (*Continued*)

Case No.	Course	Sputum Cultures		Remarks
		Before Treatment	After Treatment	
28	1	Hemolytic Strep. Non-hemolytic Strep. Staph. aureus	B. coli B. aerogenes Occasional Staph. aureus	Failed to improve on previous course of 4,000,000 units I.M. penicillin. Sustained improvement on continuous penicillin aerosol therapy prior to LLL lobectomy. Uneventful postoperative course on I.M. penicillin. Follow-up of 6 months unremarkable
29	1	Staph. aureus	Staph. aureus	Advanced bilateral bronchiectasis. Unable to continue therapy because of dyspnea and general weakness, despite bronchodilator adjuvants. To be tried later with mask-nebulizer apparatus
30	1	D. pneumoniae Staph. aureus	Staph. aureus B. coli	Advanced cylindrical and saccular bilateral bronchiectasis. Relapsed in all symptoms whenever therapy was interrupted for longer than one week, despite substitution of 10% sodium sulfacetimide aerosol. Intermittent reactions of sore tongue and irritative cough on calcium salt. No reaction to crystalline sodium salt
	2	Gram-neg. bacilli	Gram-neg. bacilli	Status quo maintained on 15% sodium sulfacetimide aerosol 1 cc. t.i.d. for 4 weeks
31	1	Hemolytic Strep. Staph. aureus	B. aerogenes Few Staph. aureus	Sustained improvement on continuous therapy at home preliminary to lobectomy of RLL with decreased cough and expectoration, sputum losing foul odor and much of purulent element. Developed postoperative foul empyema with bronchopleural fistula requiring thoracotomy for drainage 2 weeks later. Spiking febrile course subsided 3 days later. Discharged to be followed in surgical OPD 6 weeks after admission with sinus tract still open but only slight drainage. Mild residual cough and expectoration persist
	2	None	Gram-neg. bacilli	
32	1	Strep. viridans Staph. albus Non-hemolytic Strep.	Strep. viridans N. catarrhalis Gram-neg. bacilli	Past history of aspirated tack in childhood removed by bronchoscopy. Repeated hemoptyses led to admission. Bronchography following bronchoscopy demonstrated bronchiectasis of RLL and of one posterior segment of LLL. Continued penicillin aerosol therapy at home following discharge. Sustained improvement for 2 months with diminished cough and expectoration. Sputum became mucoid in consistency
33	1	Hemol. Staph. aureus	Hemol. Staph. aureus	Acute episode of diffuse bilateral bronchopneumonia caused by hemolytic Staph. aureus resistant to penicillin in concentration of 5 U/cc. Marked progressive improvement after substitution of aerosol for I.M. penicillin given for first week by continuous aerosol drip. Staph. aureus reappeared when 15% sulfacetimide aerosol was substituted and disappeared again when combined penicillin and sulfacetimide aerosol was instituted with 4 inhalations daily
	2	Hemol. Staph. aureus	Gram-neg. bacilli	

TABLE V (*Continued*)

Case No.	Course	Sputum Cultures		Remarks
		Before Treatment	After treatment	
34	1	Hemolytic Strep. Strep. viridans (Bronchoscopic aspiration)	Hemolytic gram-neg. bacilli	Advanced saccular bronchiectasis of both lower lobes resulting from unresolved pneumonia coincident with aspiration of chicken bone 5 years ago. Foreign body not visualized on repeated bronchoscopies, but was coughed up 4 years ago at time of single hemoptysis. Intratracheal instillation of penicillin 2 years ago without appreciable benefit. Temporary improvement on short course of I.M. penicillin. More striking improvement on aerosol therapy, sputum decreasing from 6 ounces daily of foul purulent material to 3–4 ounces daily of non-foul thinner sputum with less cough and dyspnea. Streptomycin aerosol to be combined with penicillin in near future
35	1	Staph. aureus	Gram-neg. bacilli Few Staph.	Marked decrease in dyspnea, cough and expectoration, sputum diminishing from over 1 ounce daily to less than ½ ounce, becoming less purulent and losing foul odor

* Nose culture.
† Throat culture.

than a three-hour period are surrounded by ice in a bowl to prevent loss of penicillin activity.

Bobrowitz, Edlin et al.[38] reported similar penicillin sputum levels after intratracheal instillation or nebulization of penicillin, but did not find sputum levels after intramuscular administration of penicillin except in one case in which the level was only 0.4 units per cc. White[39] reported no detectable penicillin sputum level after intramuscular administration.

An interesting study by Humphrey and Joules[27] revealed that penicillin was rarely found in the sputum in cases of bronchitis and bronchiectasis after intramuscular injection of the drug whereas it was present in considerable quantities after inhalation of penicillin aerosol for periods of six hours or more. These authors report that in patients with lobar pneumonia, small amounts of penicillin were recovered from the sputum after intramuscular injection during the active phase of the disease; but when the consolidation cleared and a chronic bronchitis persisted, no penicillin could be detected after intramuscular injection of penicillin, although the patient continued to cough up considerable amounts of expectoration.

We are continuing studies on penicillin sputum levels to compare values obtained with identical dosage of penicillin aerosol and penicillin by intramuscular injection in the same patients.

The problem of penicillin-resistant microorganisms has not yet become alarming in patients treated by aerosol therapy over prolonged periods, except in some instances of Staphylococcus aureus infection in children with pancreatic disease reported by Andersen and di St. Agnese.[24]

The use of various sulfonamide aerosols for eradication of gram-negative organisms

has been disappointing in our experience, but further trials with larger dosage are in progress. Recently we have been using streptomycin aerosol in cases of mixed infection or in cases showing original predominance of gram-negative bacteria. Sputum streptomycin levels are demonstrable after inhalation of the drug, but not after intramuscular injection in the small series studied thus far. Olsen[22] has shown that some cases of bronchiectasis respond better to a combination of penicillin and streptomycin aerosol.

One of our patients developed an antipenicillin substance in her serum after one year of sporadic penicillin aerosol therapy for sinusitis and infectious bronchial asthma. Since she originally obtained fairly constant blood levels of 0.05 to 0.2 unit per cc. serum after inhalation of 50,000 units, and later no blood bacteriostatic activity, her serum was tested with known amounts of added penicillin. It was found that the added penicillin was completely inhibited. The antipenicillin substance was not affected by a temperature of 60°C., but was destroyed at a temperature of 80°C. No antipenicillin substance was found in this patient's sputum, since she obtained a penicillin sputum level as high as 1,280 units per cc. for one hour after inhalation of 50,000 units. She has recently improved markedly after two weeks' treatment with nasal penicillin aerosol and intermittent negative pressure for exacerbation of chronic sinusitis. Ten other patients who have received prolonged penicillin aerosol therapy, as well as three control subjects have had their sera tested, but none have shown evidence to date of antipenicillin activity.

The clinical results of penicillin aerosol in therapy of bronchiectasis and its effect on sputum cultures are seen in Tables IV and V. Of fifty-nine courses of therapy in thirty-five patients, twenty-six of whom had bilateral disease with involvement of two or more lobes, there was marked improvement in fifteen, moderate in twenty-two, slight in fourteen and no improvement in eight. Only four patients were considered operable. These cases showed marked or moderate improvement on preoperative penicillin aerosol, but one developed a postoperative empyema despite instillation of penicillin into the pleural cavity at operation and use of postoperative intramuscular penicillin. The remaining five had disease minimal enough to warrant further follow-up on conservative treatment, and to date have continued to do well. Where sputum cultures were compared before and after courses of penicillin aerosol therapy, gram-negative bacilli predominated in forty-three with disappearance of the original gram-positive organisms, whereas only thirteen showed the presence of some gram-positive organisms after treatment.

Tables VI and VII show the clinical results and sputum cultures in penicillin treatment of eight patients with lung abscess. Of seven courses of therapy in five patients with the diagnosis of acute lung abscess, marked improvement occurred in four, slight improvement in two, and no improvement in one. Four of the five patients had complete clinical and *x*-ray recovery, whereas one required surgical drainage which was followed by recovery. Of four courses of therapy in three patients with chronic lung abscess, two resulted in marked improvement, one in slight improvement, and one showed no change. The latter patient later had a lobectomy. The one patient who twice showed marked improvement on penicillin aerosol therapy has remained well for seven months. The final outcome of the patient showing only slight temporary improvement is not known. Sputum cultures showed gram-positive organisms prior to penicillin treatment and gram-negative bacilli after treatment.

Results of penicillin therapy in treatment

TABLE VI

CLINICAL RESULTS OF PENICILLIN THERAPY IN LUNG ABSCESS

Case No.	Age	Sex	Type	Additional Diagnosis	Course	Clinical Improvement Due to Penicillin	Administration of Penicillin		
							Route	Total Dosage	Duration (Weeks)
1	35	F	Acute	Rheumatic heart disease	1	slight	I.M.	4,480,000	4.2
				Pulmonary infarction	2	marked	I	1,600,000	1.1
2	43	M	Chronic	Bronchiectasis Pulmonary fibrosis	1	slight	I	740,000	1
3	24	M	Chronic	Bronchiectasis	1	none	I	6,000,000	4.2
4	61	M	Acute	Suppurative bronchopneumonia	1	marked	I	1,600,000	1.1
5	65	M	Acute	Bronchiectasis	1	slight	I	2,650,000	1.5
					2	none	I	5,875,000	2.3
							I.M.	2,030,000	4
6	40	F	Acute	None	1	marked	I.M.	3,360,000	3
							I	6,250,000	3.5
7	16	M	Acute	Suppurative bronchopneumonia	1	marked	I.M.	8,000,000	3.5
							I	15,200,000	6.5
8	45	M	Chronic	None	1	marked	I	1,000,000	1.5
					2	marked	I	3,000,000	3

I—Inhalation.
I.M.—Intramuscular.

TABLE VII

EFFECT OF PENICILLIN THERAPY ON SPUTUM CULTURES IN LUNG ABSCESS

Case No.	Course	Sputum Culture		Remarks
		Before Treatment	After Treatment	
1	1	Hemolytic Staph. aureus	None	Abscess persisted on I.M. penicillin. Recovery with aerosol, although I.M. penicillin given later because of a second small pulmonary infarct
2	1	Strep. viridans	No Strep.	Slight increase in vital capacity. Chest *x*-rays unchanged
3	1	Hemolytic Strep.	B. proteus	Aerosol preoperatively. Lobectomy necessary, with subsequent recovery
4	1	Hemolytic Staph. aureus Strep. viridans	B. aerogenes	Previous courses of I.M. penicillin for 1 month, with increasing pneumonitis. Improvement began on aerosol therapy, and recovery occurred on combination of aerosol and I.M. penicillin
5	1	Strep. viridans	None	Moderate symptomatic improvement, but *x*-rays unchanged. Required surgical drainage of abscess with subsequent recovery
	2	Strep. viridans	B. aerogenes	
6	1	Strep. viridans	None	Slow improvement until penicillin was nebulized with helium-oxygen mixture, following which recovery occurred, with complete *x*-ray clearing
7	1	Staph. albus Strep. viridans Hemolytic Staph. aureus	B. coli B. aerogenes	No improvement on I.M. penicillin alone. Improvement began on aerosol therapy, but was most striking when 3 weeks later helium-oxygen mixture was used to nebulize penicillin, after demonstration of a nonaerated right middle lobe by bronchoscopy and bronchography. Complete *x*-ray clearing, without residual abscess cavity or bronchiectasis by lipiodol studies
8	1	D. pneumoniae	B. aerogenes	Recurrence of cough and expectoration 6 weeks after first course. Symptomatic improvement and progressive *x*-ray clearing as result of second course. No recurrence in 7 months
	2	Hemolytic Strep. Strep. viridans	Strep. viridans	

of sixteen patients in whom the primary diagnosis was chronic bronchitis are shown in Tables VIII and IX. Of twenty-four courses were obtained after penicillin treatment gram-positive organisms were still present in only three cases, whereas the others showed

TABLE VIII

CLINICAL RESULTS OF PENICILLIN THERAPY IN CHRONIC BRONCHITIS

Case No.	Age	Sex	Additional Diagnosis	Course	Clinical Improvement Due to Penicillin	Administration of Penicillin		
						Route	Total Dosage	Duration (Days)
1	57	M	.....	1	marked	I	2,240,000	12
2	36	F	.....	1	none	I	1,230,000	7
				2	none	O	7,400,000	15
3	66	F	Acute pharyngitis	1	moderate	I	300,000	3
4	35	F	.....	1	moderate	I	3,500,000	18
						I.M.	3,200,000	14
5	46	M	Pneumonitis	1	marked	I	1,300,000	7
						O	5,700,000	10
6	62	M	Chronic sinusitis	1	moderate	S.C.	1,260,000	8
			Pulmonary fibrosis			I.M.	2,230,000	11
			Pulmonary emphysema			I	2,550,000	
7	52	M	Chronic sinusitis	1	none	I.M.	2,715,000	22
						I	5,500,000	11
8	16	M	Chronic sinusitis	1	marked	I.M.	1,000,000	5
						I (N.S.)	2,700,000	8
9	15	M	Chronic sinusitis	1	marked	I (N.S.)	8,325,000	23
						I.M.	3,010,000	25
				2	marked	I (N.S.)	1,600,000	8
10	70	M	Acute bronchitis	1	slight	I	2,650,000	6
			Chronic sinusitis			O	4,900,000	9
11	58	F	Chronic sinusitis	1	marked	I	3,000,000	10 months
			Pulmonary emphysema					
				2	marked	I	1,500,000	10
12	53	M	Pulmonary tuberculosis	1	marked	O	5,000,000	10
				2	marked	I.M. (beeswax)	2,100,000	7
13	78	M	.....	1	marked	I	3,800,000	19
14	73	M	.....	1	moderate	I	2,000,000	10
				2	moderate	I	2,000,000	8
						O	1,250,000	8
15	24	F	.....	1	moderate	I	1,000,000	7
				2	moderate	I	1,500,000	10
						I.M.	1,000,000	
				3	moderate	I	2,000,000	10
						I.M.	1,400,000	
16	30	M	Chronic sinusitis	1	marked	I (N.S.)	500,000	2
				2	marked	I	1,400,000	2

I—Inhalation.
I.M.—Intramuscular.
O—Oral.
I (N.S.)—Inhalation (nasal suction).

of therapy, improvement was marked in twelve, moderate in eight, slight in one, while three resulted in no improvement. In fifteen courses in which sputum cultures gram-negative bacilli predominating.

Detailed case reports with illustrative chest *x*-ray photographs are presented below:

TABLE IX

EFFECT OF PENICILLIN THERAPY ON SPUTUM CULTURES IN CHRONIC BRONCHITIS

Case No.	Course	Sputum Culture		Remarks
		Before Treatment	After Treatment	
1	1	Pneumococcus, type 6	None	Previous course of I.M. penicillin ineffective. No recurrences for 18 months
2	1	Strep. viridans	Strep. viridans	Reaction: sore, reddened tongue and throat. Recurrent bronchopneumonia but bronchography negative
	2	Strep. viridans	None	
3	1	Hemolytic Strep.	No hemolytic Strep.	Rapid improvement
4	1	None	B. aerogenes	Bronchial relaxation relieved bronchospasm which developed after discharge from hospital
5	1	Pneumococcus, type 17	B. aerogenes	No recurrence in 1 year
6	1	Strep. viridans	B. aerogenes	Recurrent pneumonitis cleared entirely. No recurrence for over 1 year
7	1	Hemolytic Strep. Strep. viridans H. influenzae	B. aerogenes	Reaction: increased cough and bronchospasm
8	1	B. proteus	B. aerogenes	Possible bronchiectasis (bronchography refused)
9	1	Staph. albus	B. aerogenes	Probable bronchiectasis (bronchography refused). Required bronchial relaxation program on first admission. Improvement sustained over 1 year
	2	Strep. viridans	B. coli	
10	1	No growth	B. aerogenes B. coli	Reaction: sore, red tongue and throat, increased cough temporarily. Marked improvement from bronchial relaxation program
11	1	Strep. viridans Staph. aureus	Strep. viridans	Possible bronchiectasis (refused bronchography). Symptoms controlled by 1–2 inhalations weekly in clinic. Improved on aerosol therapy at home, following exacerbation of symptoms
	2	Staph. aureus Strep. viridans	Gram-neg. bacilli	
12	1	Hemolytic Strep.	B. proteus	Recurrence 6 months later
	2	Hemolytic Strep. Staph. aureus	None	Reaction: Urticaria. No recurrence in 6 months
13	1	Strep. viridans Staph. albus	None	Bronchial relaxation very beneficial. No recurrence in 6 months
14	1	Hemolytic Strep. D. pneumoniae	N. catarrhalis	Bronchial relaxation helpful. Recurrence of moderate degree later. Reaction: sore reddened tongue on calcium penicillin, but not on crystalline sodium penicillin
	2	Hemolytic Strep.	Strep. viridans	
15	1	Hemolytic Strep. Strep. viridans	None	Gradual recurrence of symptoms. Mild bronchospasm. Continued to improve on subsequent courses
	2	Staph. aureus H. influenzae	None	
16	1	Staph. aureus Hemolytic Strep. Non-hemolytic Strep.	Gram-neg. bacilli	Sinusitis remained improved, although chronic cough and expectoration persisted. Bronchography failed to demonstrate bronchiectasis despite suggestive history and persistent rales over left lower lobe. Symptoms partially relieved by occasional test inhalations and markedly relieved by longer course of therapy
	2		Gram-neg. bacilli	

CASE REPORTS

CASE 1. (C. A.). The patient, a nineteen year old man, had chronic cough and expectoration and symptoms of mild, chronic sinusitis since the age of nine years. His past history included pertussis and bronchial asthma in early childhood. Three years ago symptoms became more severe, sputum increasing in amount to 3 to 4 ounces daily of yellowish-brown purulent, occasionally blood-streaked material. Two years ago a single hemoptysis occurred of 8 ounces of bright red blood.

Bronchoscopy and bronchography in January, 1945, demonstrated advanced bronchiectasis of the right middle lobe and left lower lobe and early bronchiectasis of the right lower lobe. Surgery was suggested but refused.

On admission to the hospital two months later the patient did not appear ill. The vital signs were normal. Positive physical findings included slight congestion of the nasal mucosa, moderate injection of the pharynx and shotty posterior cervical lymph nodes. Chest appeared symmetrical with good bilateral expansion. Lungs were hyperresonant anteriorly above the level of the fourth rib and resonant elsewhere, with no change in breath sounds or fremitus. There were numerous coarse and medium moist râles over the left lower lobe and a moderate number of similar râles at the right posterior base and over the right middle lobe. The extremities showed moderate clubbing.

Laboratory data revealed the following: Red blood cells 5,700,000; hemoglobin 16.7 Gm.; white blood cells 14,100 with a normal differential count. The sedimentation rate was normal. Sputum culture: Staph. albus predominating.

Intensive combined penicillin therapy was instituted in conjunction with postural drainage twice daily. Intramuscular penicillin was given in dosage of 50,000 units every three hours for a total of 4,350,000 units. Calcium penicillin aerosol was given with the usual mouth inhalation apparatus, 50,000 units in 1 cc. normal saline every four hours for a total of 2,800,000 units. Penicillin blood levels obtained after single test inhalations were: 0.1 U/cc. serum one-half hour after start of inhalation, 0.05 U/cc. serum at one, one and one-half and two hours. The urinary excretion of penicillin in the six hours following inhalation was 13 per cent of the amount administered. At the onset of therapy the patient was raising 5 to 6 ounces daily of purulent, slightly foul, blood-streaked sputum, half of which was raised on postural drainage. After a few days cough and expectoration decreased about 50 per cent and the sputum lost its odor, becoming thinner in consistency with rare streaks of blood. Sputum culture: B. aerogenes predominating, no Staph. albus. Râles persisted especially over the left lower lobe but were less coarse and less numerous. The patient was afebrile and ambulatory. On the eleventh day the patient developed generalized urticaria necessitating cessation of all penicillin therapy. The reaction subsided in four days. The patient was discharged moderately improved to continue on a regimen of oral sulfadiazine and neosynephrine-sulfathiazolate by inhalation.

Following discharge the patient worked at a newsstand and did fairly well clinically until six months later when cough and expectoration increased following an acute respiratory infection. He was readmitted for further antibiotic aerosol therapy. Sputum culture: Hemolytic streptococci predominating. Complete blood count and sedimentation rate were normal. Râles persisted at both lung bases.

He was given a course of crude streptomycin aerosol, 200,000 units in 4 cc. distilled water twice daily for a total of 2,800,000 units in one week. No blood level was detected with this dose, but a blood level of 1.5 U/cc. serum was obtained five hours after the start of a test inhalation of 400,000 units. Sputum specimen obtained before the usual 200,000 units dose showed H. influenzae and N. catarrhalis and a few colonies of non-hemolytic streptococci on culture, whereas a specimen obtained after inhalation showed only a moderate growth of non-hemolytic streptococci.

Following the course of streptomycin aerosol, penicillin aerosol was given for fifteen days with a daily dosage of 225,000 units or a total of 3,525,000 units. Penicillin blood levels comparable with those on the first admission were obtained. Final sputum culture: B. aerogenes. Sputum had decreased from 3 ounces to 1 ounce

daily at the time of discharge from the hospital.

In the next interval of seven months at home the patient took daily penicillin aerosol inhalations 50,000 units three times a day for a total of 30,000,000 units.

At the end of this period he was hospitalized for re-evaluation. Sputum cultures: B. aerogenes or E. coli predominating. Physical signs over the left lower lobe were unchanged, but only a few fine and medium post-tussic râles were audible at the right posterior and anterior bases. Sputum measured 2 to 3 ounces daily of purulent, non-foul, non-bloody material. Sinus *x*-rays revealed mild maxillary and ethmoid sinusitis. Bronchography was repeated and reported as showing cylindrical bronchiectasis of the left lower lobe only, although the right middle lobe was not completely filled. It was believed that there possibly was slight improvement in the bronchographic findings, despite difference in technic, compared with the earlier films.

Since the patient's family still refused any surgical procedure, a course of calcium penicillin aerosol, 50,000 units dissolved in 1 cc. of 0.25 per cent parachlorophenol five times daily was given over an eighteen-day period for a total of 4,250,000 units. During the last five days an additional 50,000 units was given four times daily by the nasal aerosol-negative pressure apparatus for a total of 1,000,000 units. Sputum culture showed only a few colonies of gram-negative bacilli, which were sensitive to a 1:2,000 dilution of para-chlorophenol. At the start of therapy using para-chlorophenol as a diluent, the patient complained of increased dry, irritative cough which later subsided. Sputum decreased to 1 to 1.5 ounces daily, and the patient was discharged improved. He has continued aerosol therapy at home using penicillin dissolved in normal saline for the past five months, continuing to work without any exacerbation of symptoms.

Case 2. (M. R.*). The patient, a twenty-one year old white man, had advanced bilateral bronchiectasis, pulmonary emphysema and bronchial asthma dating back to childhood. Symptoms became more severe after the age of fourteen years. Bronchograms demonstrated marked cylindrical and saccular bronchiectasis of both lungs. (Fig. 5.) Chest *x*-ray (Fig. 5) prior to institution of continuous penicillin aerosol therapy showed persistent peribronchial pneumonitis. The patient failed to obtain any sustained improvement on a regimen of postural drainage, regular bronchoscopic aspirations, oral sulfonamides, repeated courses of intramuscular penicillin, oral penicillin and intermittent courses of penicillin aerosol and various sulfonamide aerosols. Numerous hospitalizations were necessary.

Since June, 1945, the patient has been on continuous calcium penicillin or crystalline sodium penicillin aerosol therapy at home, followed in the out-patient department with a daily dosage of 200,000 units divided into four inhalations. He began to show improvement after the first six weeks, since when clinical improvement has been more or less progressive and sustained. Test penicillin blood levels after inhalation of 50,000 units show 0.05 U/cc. serum at the end of one-half hour, 0.05 U/cc. at one hour, and 0.025 U/cc. at two hours. Figure 6 shows chest *x*-rays taken after institution of aerosol therapy with marked clearing after four months on continuous therapy and less striking *x*-ray improvement at the end of sixteen months. The clinical improvement, however, has been striking throughout the eighteen-months course thus far. Cough is rarely troublesome and is productive of only 1 to 2 ounces mucopurulent material daily compared to the original amount of 8 ounces purulent sputum daily. Sputum cultures generally show only gram-negative bacilli, although rarely Strep. viridans or Staph. aureus have been cultured. There has been a weight gain of 35 pounds. Asthma has not been troublesome, rarely requiring use of the Vaponefrin spray or oral aminophyllin. Mild activity does not produce dyspnea, whereas prior to treatment the patient could not walk across the room without dyspnea. Vital capacity has increased from 1,200 to 2,200 cc. During the past seven months the patient has worked four hours daily, as a clerk, for the first time in his life.

Despite the prolonged use of penicillin the

* This case was previously reported in part by the authors in the New York State J. Med., 46: 1703, 1946.

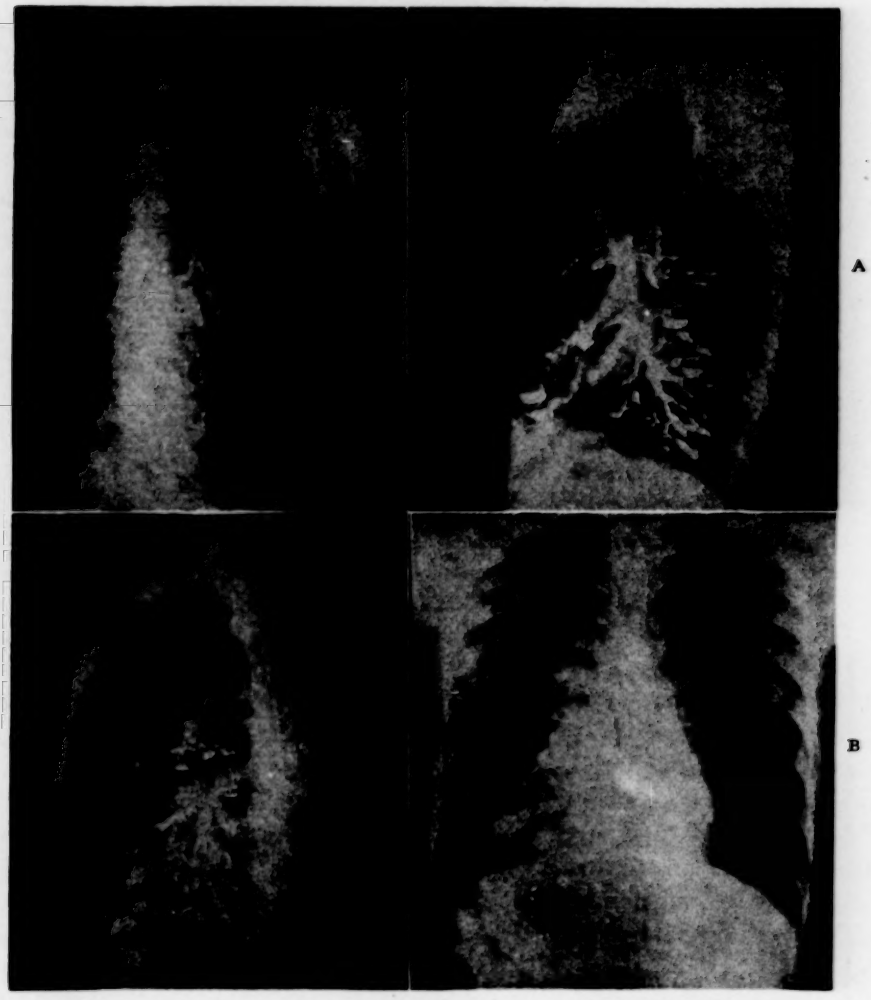

FIG. 5. Case 2. A and B, bronchograms in 1944 revealing advanced cylindrical and saccular bronchiectasis of all lobes. Chest *x*-ray (bottom right) in 1944 prior to continuous penicillin aerosol therapy, demonstrating bilateral peribronchial pneumonitis, pulmonary fibrosis and emphysema.

gram-positive organisms occasionally obtained on sputum culture have not become penicillin-resistant. Attempts to lower the daily dosage below 200,000 units have resulted in increased cough and expectoration within five to seven days. Attempts to substitute 15 per cent sodium sulfacetimide aerosol have likewise resulted in exacerbation of symptoms within ten days, with gram-positive organisms reappearing on culture of the sputum. Since E. coli cultured from his sputum was shown to lessen the growth-inhibiting power of penicillin by 40 to 50 per cent in two hours, 1 cc. of 15 per cent sodium sulfacetimide has been added to each inhalation of penicillin aerosol for six months, without effect on the presence of gram-negative bacilli. Subsequently 1 cc. of 30 per cent sodium sulfacetimide was added to the penicillin aerosol without eradication of gram-negative bacilli from the sputum.

At the time of the last chest *x*-ray (Fig. 6) considerable puddling of secretions in the cystic areas was noted. Physical examination revealed occasional expiratory rhonchi toward the right base, numerous coarse and medium moist râles persisting over the lower half of the right chest and fewer finer râles over the lower half of the left chest. The patient was advised not to neglect postural drainage on arising and retiring and started taking aminophyllin 0.2 Gm. on arising

FIG. 6. Case 2. Chest *x*-ray (left) taken four months after institution of continuous penicillin aerosol therapy reveals marked clearing of pneumonitis secondary to bronchiectasis. Chest *x*-ray (right) taken one year later shows less marked clearing with some retention of secretions in cystic areas in right lower lung field.

and at night when necessary. The patient's blood serum shows no antipenicillin activity despite prolonged therapy. Penicillin sputum level was 640 U/cc. for one hour after inhalation of 50,000 units. One week ago streptomycin aerosol (2 Gm. daily) was substituted for penicillin aerosol for a course of therapy, sodium sulfacetimide being discontinued. A twenty-four-hour sputum assay revealed 280 units streptomycin per cc. 17,640 units total streptomycin activity in 63 cc. sputum.

CASE 3. (H. C.). The patient, a sixteen year old white boy, had a history of chronic sinusitis and chronic bronchitis since early childhood. At the age of nine years bilateral permanent antral openings were established without sustained improvement. From the age of fourteen to fifteen years the patient had severe exacerbation of symptoms with increase in sputum to 4 to 6 ounces daily of purulent and mucopurulent material, rarely blood-streaked and slightly foul on one occasion, progressive dyspnea accompanied by asthmatic attacks, and a weight loss of 37 pounds. A week's course of intramuscular penicillin in August, 1944, resulted in no improvement. Residence in Arizona afforded slight temporary improvement until May, 1945, when the patient returned to New York City because of progressive symptoms. Bronchograms made in the Spring of 1945 were said to show bronchiectasis. A two weeks' course of oral penicillin had no effect.

On admission to the hospital July 20, 1945, the patient appeared acutely and chronically ill, with evidence of marked weight loss. His temperature was 103°F., pulse 110, respirations 26, blood pressure 90/60. Significant physical signs: The nasal septum was deviated to the right with purulent nasal and post-nasal discharge; there were shotty posterior cervical lymph nodes. The chest revealed more prominence of the right side anteriorly with fair bilateral expansion. There were scattered moist coarse and medium râles at the left posterior base and a few inspiratory rhonchi. Extremities showed early clubbing.

Laboratory data revealed the following: Red blood cells 4.7, hemoglobin 13.3 gm., white blood cells 19,600 with polymorphonucleus 85, lymphocytes 8, monocytes 7. Sputum culture: Staph. albus predominated. Sinus *x*-rays: There was marked thickening of the lining membrane of both antra with clouding of the ethmoids. Bronchoscopy revealed left main bronchus suspicious of chronic inflammation. Chest *x*-rays after lipiodol instillation failed to demonstrate bronchiectasis on the left and the right side

was not visualized. Skin tests showed numerous food sensitivities.

The patient ran a spiking febrile course to 103°F. with occasional chills and profuse sweats for five days, when penicillin therapy was instituted. Sodium penicillin was given intramuscularly, 15,000 units every three hours for a total of 3,010,000 units. Calcium penicillin nasal aerosol with alternating negative pressure was started at the same time, 75,000 units in 3 cc. normal saline five times a day, preceded by privine nose drops, for a total of 8,325,000 units. Within a few days there was marked improvement, temperature ranging around 100°F. and sputum diminishing to 2 ounces of mucopurulent material daily. Dyspnea and wheezing disappeared. The lungs became clear to physical examination. Subsequent sputum cultures showed B. aerogenes or E. coli predominating. The white blood count was normal. Penicillin blood levels after test mouth inhalation of 50,000 units in 1 cc. normal saline were: 0.1 U/cc. serum at the end of one-half hour; 0.05 U/cc. serum at the end of one hour; 0.01 U/cc. at the end of two hours. The patient gained 10 pounds during his hospital stay of five weeks and had a submucous resection performed toward the end without complications. He was discharged markedly improved.

The patient returned to the hospital seven months later because of increased cough and expectoration, following an acute sinusitis, for another course of nasal penicillin aerosol with alternating negative pressure. At this time the lungs were clear. The patient was ambulatory, afebrile and had gained 25 pounds in the interim. Sputum cultures showed hemolytic staphylococcus aureus predominating. After a total of 2,500,000 units of calcium penicillin aerosol in thirteen days, the patient was discharged from the hospital improved.

He was re-admitted to the hospital August 30, 1946, with a diffuse bilateral bronchopneumonia. (Fig. 7.) Hemolytic staphylococcus aureus was repeatedly cultured from his sputum. Blood cultures were negative. Leukocytosis persisted. Originally, he was on a regimen of intramuscular penicillin, having received a total of 1,000,000 units in one week prior to admission, with daily dosage gradually being increased from 250,000 units to 2,000,000 units by the end of the first week in the hospital. After nine days in the hospital the dosage was raised to 4,000,000 units daily for ten days by intramuscular injection. During this intensive course of intramuscular penicillin therapy, the patient remained in an oxygen tent, temperature fell from original range of 102 to 105°F. to 100 to 102°F. but tachycardia and dyspnea persisted, respirations ranging between 34 and 50 per minute. Expectoration averaged 8 to 12 ounces daily of yellowish purulent sputum. Hemolytic staphylococcus aureus was found to be resistant to 5 units of penicillin per cc. and 10 units of streptomycin per cc. At this time, nineteen days after admission, chest *x*-ray revealed only slight clearing. (Fig. 7.) The lungs continued to show numerous coarse and medium moist râles bilaterally with some inspiratory and expiratory rhonchi.

Intramuscular penicillin was discontinued and crystalline sodium penicillin aerosol was started by continuous slow drip into a nebulizer within an oxygen head tent. A daily dosage of 1,000,000 units in 100 cc. normal saline was given over a twenty-four-hour period for seven days. The only additional change in therapy was the use of intravenous aminophyllin 0.24 Gm. daily for three days, and nebulized 1 per cent neosynephrine and Vaponefrin, 0.5 cc. of each three times daily. By the second day of treatment the patient began to show improvement. Bronchodilator drugs were not necessary after the third day, although use of neosynephrine was continued. Bronchoscopy on the fourth day revealed creamy exudate coming from all bronchi which showed edematous reddened mucosa. Culture of aspirated specimen showed B. coli only. Daily sputum cultures gradually showed diminution in number of hemolytic staphylococcus aureus colonies and their final disappearance, although the penicillin blood level was only 0.025 U/cc. serum. Gram-negative bacilli predominated on sputum cultures. Temperature ranged between 99 and 100.4°F. Cough decreased markedly and sputum became chiefly mucopurulent in character, measuring 3 to 4 ounces daily, a decrease of over

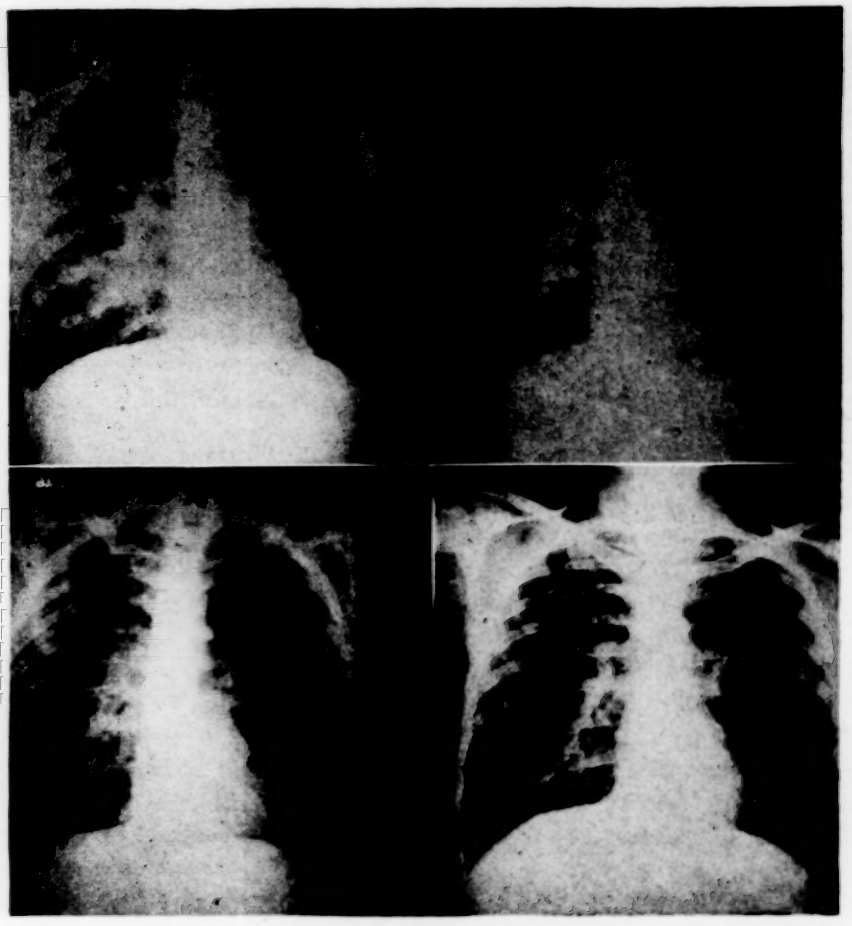

FIG. 7. Case 3. Admission chest *x*-ray (left) revealed diffuse bronchopneumonia with major involvement of the right lung and left hilar lymphadenopathy. Chest *x*-ray (right) eighteen days after admission following massive dosage of intramuscular penicillin revealed very slight improvement.
FIG. 8. Case 3. Chest *x*-ray (left) one week after penicillin aerosol was substituted for intramuscular penicillin showed moderate clearing. Chest *x*-ray (right) fourteen days later revealed further clearing of bronchopneumonia, although some enlargement of the left hilar shadow persisted as well as a diffuse bilateral fibrosis and emphysema.

50 per cent. Respirations fell to 28 to 30 per minute. A moderate number of medium moist râles persisted bilaterally posteriorly at the bases. Chest *x*-ray showed moderate clearing. (Fig. 8.) At the end of this week penicillin aerosol and the oxygen head tent were discontinued. Fifteen per cent sodium sulfacetimide aerosol, 4 cc. five times daily was substituted, using the ordinary mouth inhalation apparatus, for a total of ten days. The patient's respirations were 22 to 24 per minute; temperature remained below 100.2°F. However, hemolytic staphylococcus aureus reappeared on sputum cultures and gram-negative bacilli disappeared. Penicillin aerosol was reinstituted using the mouth inhalation apparatus, dosage of 100,000 units in 2 cc. normal saline four times daily with 1 cc. 15per cent sodium sulfacetimide added to each inhalation; 30 per cent sulfacetimide was used during the last ten days. This was continued for eighteen days or a total of 7,200,000 units. After the first four days Staph. aureus disappeared and gram-negative bacilli predominated on culture. Penicillin levels on arterial and venous blood

taken simultaneously one-half hour after the start of a test inhalation of 50,000 units penicillin showed the same level, 0.2 U/cc. serum. Venous blood levels after test inhalation of 100,000 units were 0.1 and 0.05 U/cc. serum, respectively, at the end of one and two hours. Penicillin levels in the sputum collected for eight hours after a single inhalation of 100,000 units showed 0.2 unit per cc. sputum. Penicillin level in sputum collected by encouraged coughing for ten minutes after a single inhalation of 100,000 units revealed 640 U/cc. sputum. Sensitivity of the hemolytic staphylococcus aureus was reduced to a concentration of 1.6 units per cc. during the course of penicillin aerosol therapy, compared to the original 5 units per cc. during the period of intensive intramuscular therapy.

Temperature remained below 100°F. during the last two weeks of therapy and respirations fell to 20 to 24 per minute. White blood cells fell to 14,650 with a normal differential count. ESR was 37 mm. after one hour. A chest *x*-ray revealed further clearing but evidence of persisting enlarged hilar shadows and a diffuse fibrosis. (Fig. 8.) The lungs became clear to percussion and auscultation except for occasional post-tussic basal râles. Because of emotional difficulties the patient was discharged improved after a hospital stay of eight weeks to continue penicillin aerosol treatment at home.

Case 4. (J. K.). The patient, a sixteen year old schoolboy, was admitted to the hospital February 27, 1946, complaining of cough and expectoration for three months, accompanied by intermittent fever, malaise and a weight loss of 8 pounds. He had received a short course of oral sulfadiazine at the onset of his illness with only temporary slight improvement. Sputum amounted to as much as one cupful daily of greenish yellow, purulent, non-foul material. There was a single hemoptysis of one-half cupful bright red blood in the first month, without subsequent streaking. Temperature spiked each day to 101° or 102°F. Sputum was negative for acid-fast bacilli. His past history was unremarkable except for pertussis in childhood and mild, chronic sinusitis for four years.

Examination revealed a well developed, well nourished white boy in no acute distress, but coughing occasionally. His temperature was 101.2°F., pulse 90, respirations 20, blood pressure 125/70. Positive findings were limited to the chest which showed a slight lag on the right. Over the right lung there was dullness with diminished to absent breath sounds and voice sounds anteriorly and laterally below the level of the fourth anterior rib, with fine and medium moist râles anteriorly near the midline and at the posterior base. The left lung was clear throughout.

Laboratory data revealed the following: Red blood cells 4,750,000, hemoglobin 15.5 Gm., white blood cells 15,800 with 78 per cent polymorphonuclear cells. The sedimentation rate was 57 mm. after one hour; the tuberculin test was negative. Sputum concentrates were negative for acid-fast bacilli. Sputum culture: Staph. albus predominating. Blood culture: No growth in one flask; Staph. albus in the second flask. Chest *x*-rays (Figs. 9 and 10) revealed consolidation of the right middle lobe and bronchopneumonia in the basal portions of the right and left lower lobes.

Intramuscular penicillin therapy was instituted, 40,000 units every three hours and maintained for three and one-half weeks or a total of 8,000,000 units. Bronchoscopy one week after admission revealed a non-aerating right middle lobe with markedly hyperemic and edematous bronchial mucosa. Thick purulent secretions were aspirated from the right lower lobe, culture of which yielded hemolytic staphylococcus aureus, Strep. viridans and E. coli. The patient ran a low grade fever for two weeks, following which the temperature did not rise above 100°F. Chest *x*-rays taken on March 11, 1946 (Figs. 9 and 10) showed marked contraction of the right middle lobe but no other change. Sputum had diminished to 10 cc. daily but was still purulent. Accordingly, penicillin aerosol therapy, 50,000 units four times daily was combined with the intramuscular regimen for two weeks, when the latter was stopped and the patient treated with penicillin aerosol alone, dosage being raised to 100,000 units four times daily, using the ordinary mouth inhalation apparatus, preceded by nebulization of neosynephrine and Vaponefrin. At the end of the fourth hospital week and the second week of

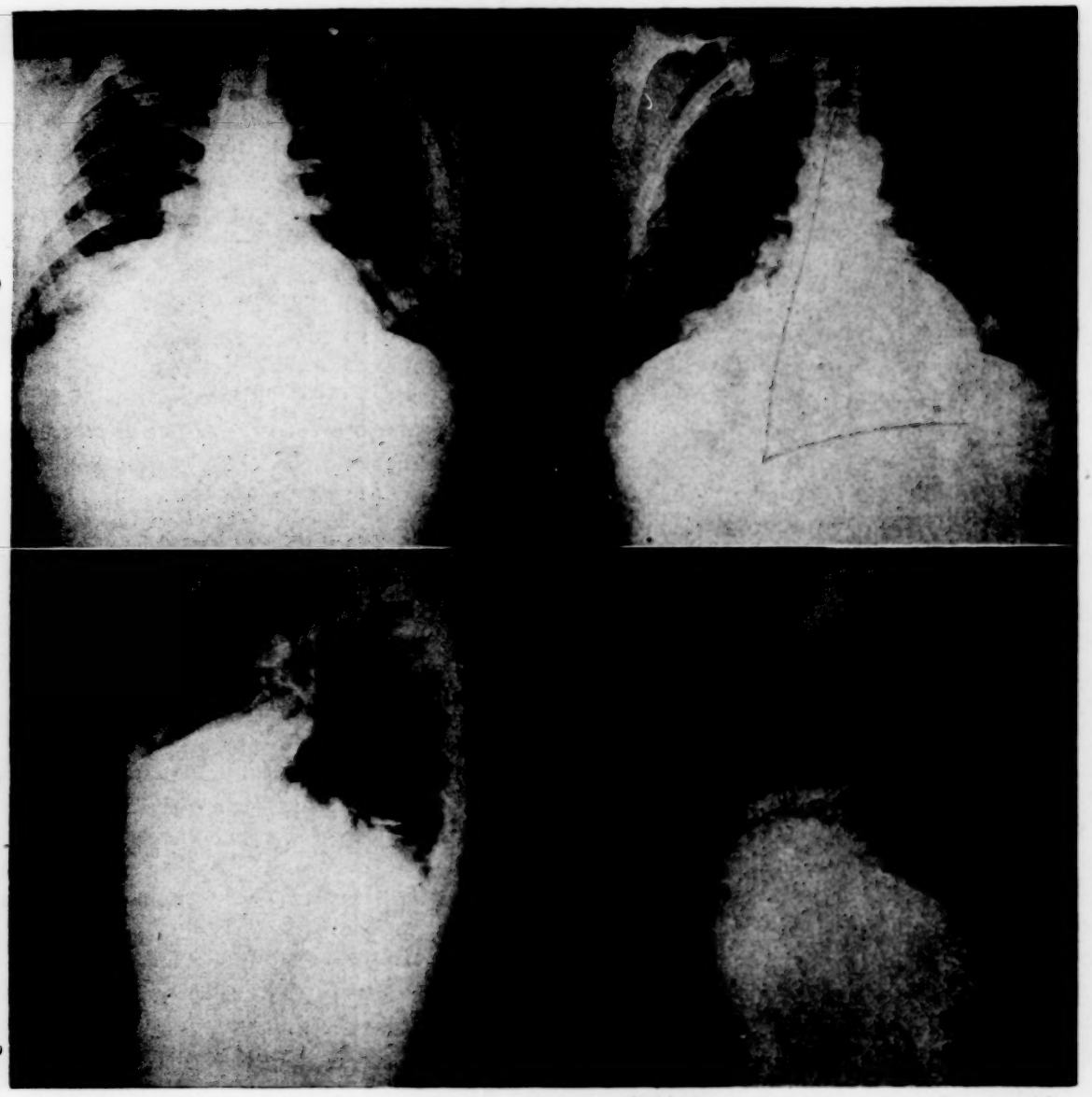

FIG. 9. Case 4. Chest postero-anterior *x*-ray on admission (left) demonstrating pneumonic consolidation of the right middle lobe and bronchopneumonia of basal portions of both lower lobes, with *x*-ray appearance (right) after twelve days of intramuscular penicillin showing slight clearing but marked shrinkage of the right middle lobe.

FIG. 10. Case 4. Chest right lateral films on admission (left) and twelve days later (right) revealing marked shrinkage of right middle lobe following initial suppuration.

aerosol therapy, bronchoscopy showed no change in the appearance of the right middle lobe bronchus, and lipiodol instilled through the bronchoscope failed to penetrate the bronchial orifice. No bronchiectasis was demonstrable in the right or left lower lobes. Repeated sputum cultures showed B. aerogenes or E. coli only.

Because of the clinical improvement and because of the finding of a non-aerated middle lobe which was the site of a suppurative process, it was decided to defer surgery until an intensive course of penicillin aerosol had been tried using 80 per cent helium 20 per cent oxygen to nebulize the penicillin to obtain better penetration into the right middle lobe by virtue of the lighter gas. Thus far the patient had received a total of 5,200,000 units of penicillin aerosol in three weeks. During the following three and

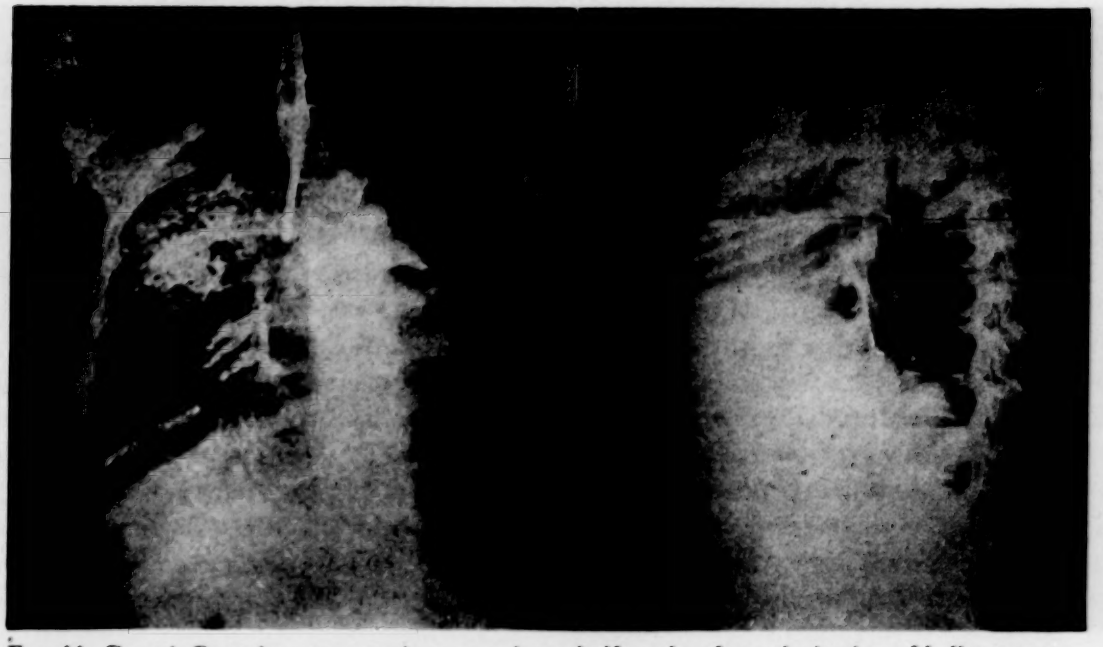

FIG. 11. Case 4. Bronchograms made two and one-half weeks after substitution of helium-oxygen mixture to nebulize penicillin aerosol show adequate filling of re-expanded right middle lobe without evidence of abscess cavity or bronchiectasis.

one-half weeks a total of 10,000,000 units penicillin aerosol was administered, 100,000 units four times daily nebulized with helium-oxygen mixture, preceded by nebulization of 1 per cent neosynephrine. The patient was ambulatory during this period and asymptomatic. A bronchoscopy two and one-half weeks after this change in regimen showed some opening of the right middle lobe bronchus with decreased hyperemia and edema. Lipiodol now penetrated into the middle lobe and failed to show either an abscess cavity or bronchiectasis. (Fig. 11.) Repeated blood level tests after inhalation of 100,000 units penicillin were negative. One week later penicillin aerosol therapy was cancelled. Physical examination was completely negative. The patient was discharged nine weeks after admission, asymptomatic with a weight gain of 25 pounds, and the follow-up period of eight months has been unremarkable.

COMMENTS

Efficient antibiotic treatment of bronchiectasis, lung abscess and chronic bronchitis requires an adequate local concentration of the drug, which in some cases is not obtained by intramuscular or oral administration. With antibiotic aerosol therapy, administered by appropriate technic effective topical application of the drug may be obtained. In penicillin aerosol therapy an adequate concentration of the drug should be present in the blood as well as in the sputum. However, some patients have shown clinical response to penicillin aerosol therapy without obtaining appreciable blood levels, while others have failed to improve on intramuscular penicillin alone despite high blood levels. An advantage of penicillin over sulfonamide aerosol therapy is that penicillin is not inhibited by para-aminobenzoic acid or purulent exudates. Only traces (0.4 to 0.9 mg. per cent) of sulfacetimide have been found in the blood after inhalation of 2 cc. of 30 per cent sodium sulfacetimide. Para-chlorophenol appears to have a toxicity which militates against its use as an antibiotic aerosol. Sulfamylon is a substance worthy of investigation since it is not affected by the presence of pus, blood or products of tissue necrosis.

It has been used by Howes[40] in local chemotherapy of wounds with encouraging results. Whether it can be safely given as an aerosol requires investigation.

Sputum cultures of patients treated with penicillin regularly show disappearance of gram-positive penicillin-sensitive organisms. During treatment and for varying periods of time after the termination of treatment, sputum cultures reveal gram-negative organisms, particularly those of the coliform group, predominating. Their pathogenic significance is not clear. However, Abraham and Chain[41] and Woodruff and Foster[42] demonstrated that these bacteria elaborate an enzyme "penicillinase" which destroys some of the bacteriostatic activity of penicillin. Further investigations are necessary to determine whether patients initially showing a mixed flora in sputum cultures should be started on combined antibiotic therapy, such as penicillin and streptomycin, or changed from one antibiotic to a combination depending on subsequent findings. With the advent of new antibiotics, more suitable combinations may be found, although the problem of development of resistant strains of bacteria must be kept in mind. Advantages of continuous therapy must be weighed against the disadvantages. Sensitivity tests should be checked when feasible at the onset of, during and after therapy, especially when it is prolonged.

Antibiotic aerosol therapy has definite advantages in chronic suppurative pulmonary disease when protracted treatment is required, because of the ease of administration in non-hospitalized patients and in children. The total daily dosage of penicillin aerosol recommended is higher than that required for intramuscular injection, generally being in the range of 150,000 to 500,000 units, although some patients have maintained original improvement on subsequent lower dosage. Relapses are the rule in cases of advanced bronchiectasis if antibiotic aerosol therapy is not continued more or less indefinitely. The dangers of inadequate treatment if low dosage or ineffective technic is employed should be kept in mind.

If the tracheobronchial tree is partially obstructed by purulent exudate or congestion and edema of the mucosa, appropriate measures must be taken to insure a patent airway so that antibiotic aerosols may be efficacious. These measures may include bronchoscopic aspiration, postural drainage, and the use of bronchodilator or vasoconstrictor drugs such as aminophyllin or vaponefrin-neosynephrine mixtures by nebulization. If there is considerable obstruction, helium-oxygen mixtures should be tried as the vehicle for antibiotic aerosols.

Systemic reactions to penicillin or to its impurities are less frequently observed with aerosol than with intramuscular administration. Antihistamine drugs such as benadryl or pyribenzamine are useful in relief of allergic reactions.

The incidence of penicillin sensitivity reactions has decreased with the use of the purer crystalline salts. We have encountered no systemic reactions using crystalline penicillin aerosol during the past six months. A few patients have developed local reactions, however, manifested by a coated, black or sore, reddened, smooth tongue. The nature of this reaction is still unknown, although it may be related to some impurities still present or to destruction of some micro-organisms present in the normal mouth flora which are responsible for the usual protective tongue coating. It occurs in susceptible individuals even if the mouth is rinsed well after inhalations. Inhalations may be resumed cautiously after the reaction subsides. The same reaction occurs in susceptible patients given oral penicillin in liquid form, regardless of the dilution. The reaction seems to clear more rapidly if patients are given large

doses of nicotinamide, and sometimes riboflavin. It is possible that the local tongue reaction occurs only in patients with subclinical nicotinamide deficiency, the deficiency subsequently becoming clinically detectable with varying severity. Ellinger and Shattock[43] have reported a case of nicotinamide deficiency following oral penicillin. Protective amounts of nicotinamide are being given to patients who previously showed this reaction to ascertain whether it can be prevented in the present course of penicillin treatment. Evidence of increase in irritative cough or bronchospasm with sensation of substernal soreness has been encountered very rarely since the use of crystalline penicillin aerosol. If these symptoms occur, therapy should be discontinued at least temporarily. When resumed, it is generally wise to employ a lower concentration of penicillin.

The importance of the high local penicillin concentration obtained in aerosol therapy has become more clearly manifested in cases with relatively resistant strains, such as the patient with pneumonitis due to Staphylococcus aureus. Further studies are in progress to determine the amount and duration of local penicillin activity following inhalations by the various techniques described as an aid in administration of adequate dosage by aerosol therapy. Sputum penicillin levels may ultimately be considered to be as significant as blood levels in the treatment of the groups of bronchopulmonary diseases under consideration.

SUMMARY

Modifications in the technic of administering antibiotic aerosols are described. Penicillin blood levels obtained after inhalation are presented. A large amount of unused penicillin remains in the apparatus. Crystalline penicillin is the preparation of choice, since fewer local or systemic reactions have been encountered with its use. Physiological saline appears to be the most satisfactory diluent for penicillin at the present time.

Attention is directed towards the importance of a high concentration of penicillin in the sputum, as well as an effective blood level, in therapy of suppurative bronchopulmonary disease. Following penicillin aerosol administration, sputum assays reveal high concentrations of the drug, whereas little or no penicillin is found in the sputum after intramuscular injection.

Sputum cultures following courses of therapy with penicillin aerosol show disappearance of penicillin-sensitive gram-positive organisms and predominance of gram-negative bacteria, usually of the coli-aerogenes group. Certain sulfonamide aerosols as well as streptomycin may be combined with penicillin in an attempt to eliminate gram-negative as well as gram-positive bacteria from sputum cultures.

Daily dosage of penicillin aerosol employed in treatment of bronchiectasis, lung abscess and chronic bronchitis varies generally from 150,000 to 500,000 units, although in a few instances 1,000,000 units are recommended.

Clinical results of penicillin aerosol therapy in thirty-five patients with bronchiectasis, eight patients with lung abscess and sixteen patients with chronic bronchitis are tabulated, and four case reports with illustrative chest *x*-rays are presented.

Of fifty-nine courses of therapy in thirty-five patients with bronchiectasis, there was marked improvement in fifteen, moderate in twenty-two, slight in fourteen and none in eight. Of seven courses of therapy in five patients with acute lung abscess, marked improvement occurred in four, slight in two and no improvement in one. Of four courses of therapy in three patients with chronic lung abscess, two resulted in marked improvement, one in

slight improvement and one showed no change. Of twenty-four courses of therapy in sixteen patients with chronic bronchitis, improvement was marked in twelve, moderate in eight, slight in one and absent in three.

Although a final appraisal of the benefit which may be expected from antibiotic aerosol therapy cannot be made at the present time, it is our conclusion that penicillin aerosol therapy constitutes an effective and practical technic which may be added to other forms of therapy in the management of patients with bronchopulmonary suppuration.

The crystalline penicillin was supplied by Commercial Solvents Corporation, the sulfacetimide by Schering Corporation, and the oxygen by the Linde Air Products Company. The nebulizers employed in the investigation were supplied by the Vaponefrin Company. An additional fund was contributed by Mr. Cornelius Crane.

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Portable Unit for Aerosol Medication

HAROLD V. DWYER, M.D.

DETROIT, MICHIGAN

THE benefit of administering various medicaments by the aerosol or inhalation method has been adequately demonstrated by Barach,[1,1a] Segal,[2] Vermilye,[3] Herrold and Nichols[4] and others. Among such substances are penicillin, streptomycin and adrenalin. Oxygen, carbon dioxide and oxygen-helium are inhaled directly or used as a vehicle for other substances through a nebulizer. The ease, convenience and freedom from pain and irritation at injection sites have been appreciated by numerous recipients. The advantages of applying these preparations

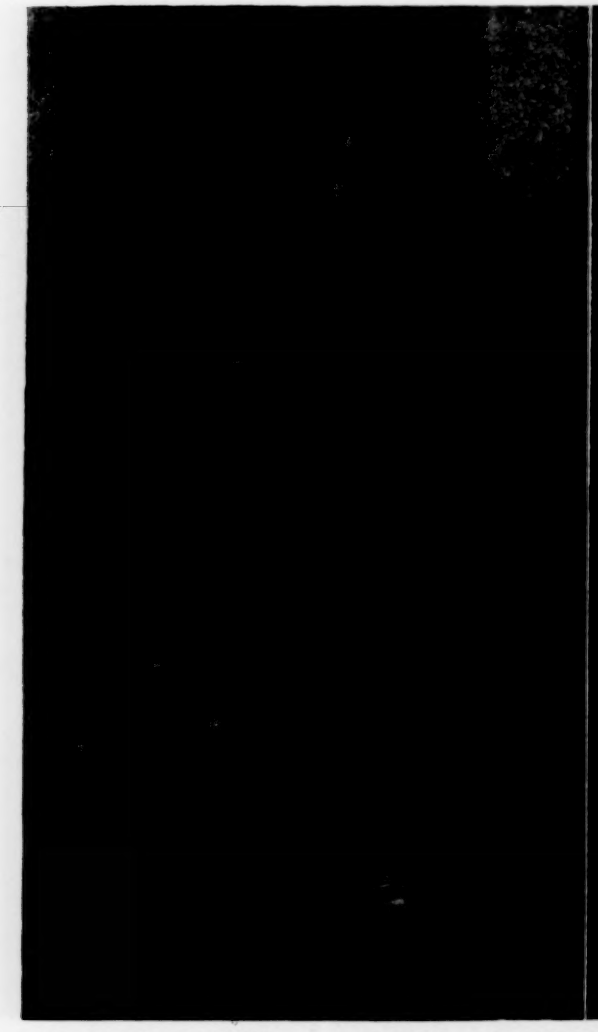

FIG. 1. The unit with case, carrying strap and accessories.

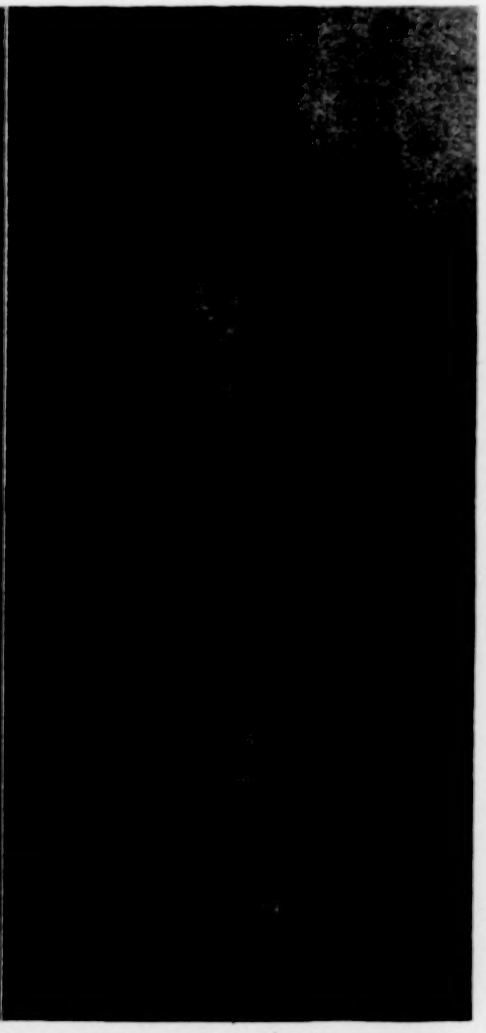

FIG. 2. Enlarged view of the working mechanism.

directly to local areas are manifest when at the same time a desired blood level is attained by absorption.

The principle drawbacks to the method are the weight and expense of the apparatus and its relative immobility. The large tanks of oxygen require two men and a truck to move them. The pressure gauge and flow-meter cost from $55.00 to $75.00 when they are available and are costly to rent. Over one-half of the gas is wasted because of shunting through the open end of a Y-tube, provided for that purpose, during expiration.

The apparatus illustrated overcomes all of these disadvantages. The tank is made of very light weight sheet metal and is encased in heavy duck material with carrying strap attached. It can be lifted or carried with two fingers of one hand, the entire apparatus weighing about 8 pounds. The capacity of the tank is sufficient for about five days' use with four inhalations a day. No oxygen or other gas is wasted. It can be carried easily while walking or riding in autos, trains, planes, buses, ambulances, etc. It can be produced for about one-quarter the cost of the larger apparatus.

Method of Operation. Opening valve A will allow gas to enter chamber B. Finger tip pressure on button C starts a flow through the flow-meter D, outlet E to the nebulizer (N) and into the mouth or through the nasal tubes into the nasal cavity. Release of pressure on C stops the flow. G is a pressure gauge which registers the amount of gas and pressure (to 500 pounds) in the tank. Valve H and cable attachment allow refilling from a large tank in twenty to thirty seconds.

The apparatus fills a distinct need for the administration of medication by the aerosol method in the home or any place where portability, lightness, low cost and ease of administration are desired. This is especially true when frequent or painful injections are not possible or well tolerated —also when the medicaments have to be administered over a long period of time in patients not required or able financially to be confined to a hospital.

FIG. 3. Size of unit compared to the standard "M" tank of oxygen.

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567 Fisher Bldg.

Therapeutic and Side Effects of Pyribenzamine and Benadryl*

A Comparative Study Based upon a Survey of Twenty-six Clinical Reports in the Literature

MARY HEWITT LOVELESS, M.D.

NEW YORK, NEW YORK

SINCE the introduction of benadryl early in 1946, and pyribenzamine during October of the same year, some twenty reports on the former and five on the latter drug have appeared in American literature with reference to allergic disorders. By fitting these 3,600 observations into diagnostic groups and adding them to 200 of our own there is adequate material for statistical evaluation of certain of the conditions under consideration. Since eight of the published articles included data on side reactions, it is also possible to draw comparisons between the types and incidence of untoward response with the two agents. This is the dual purpose of the following analysis.

MATERIAL AND METHODS

The various disorders treated with the histamine antagonists have been sorted into the diagnostic groups and subgroups listed in Tables IA and IB which indicate the number of such disturbances observed by each investigator. The general efficiency of the drugs has been appraised by determining what proportion of all trials resulted in improvement (partial or complete). Finally, the various disorders have been arranged in order of their susceptibility to benadryl and a comparison made with their response to pyribenzamine. (Table III.)

The side reactions have been listed in a similar manner for individual authors, the incidence of each type of side effect being finally estimated on the basis of group averages.

All reports dealt with adult patients with the exception of forty-three cases of Levin, all of Logan's, one of Bowen's, one of Waldbott's and two of Pinkus'. The medication was oral and the dose was usually 50 or 100 mg., repeated after some hours if necessary. For children the amount given was usually adjusted to the weight of the child.

THERAPEUTIC RESULTS

In order to simplify the presentation of therapeutic results Table III will be used as a guide, with occasional reference to detailed Tables IA, IB, IIA and IIB. Although Table III shows that the first four disorders (serum disease, "constitutional" reactions following overdosage with allergens, vasomotor rhinitis due to external, non-seasonal agents and acute urticaria) all yield extremely well to benadryl and pyribenzamine, it is obvious that the first three items cover too few cases for reliable conclusions. Chronic urticaria, hay fever and non-atopic dermatitis of vari-

* From the Department of Medicine of The New York Hospital and the Cornell University Medical College, New York, N. Y.

TABLE IA

CLINICAL EFFECTIVENESS OF HISTAMINE ANTAGONISTS IN ALLERGIC DISORDERS: BENADRYL

Investigator	Total Number of Patients	Total Number of Complaints	Allergic Rhinitis						Bronchial Asthma						Urticaria				Dermatitis	
			Extrinsic				Intrinsic		Extrinsic				Intrinsic		Acute		Chronic		Atopic	
			Seasonal		Non-seasonal				Seasonal		Non-seasonal									
			No. Complaints	No. Improved %	No. Complaints	No. Improved %	No. Complaints	No. Improved %	No. Complaints	No. Improved %	No. Complaints	No. Improved %	No. Complaints	No. Improved %	No. Complaints	No. Improved %	No. Complaints	No. Improved %	No. Complaints	No. Improved %
Bowen	65	65	...	..	...	...	(...	20)	..	...	..	...	(...	10)	18	100	29	73	6	100
Curtis, Owens	18	20	...	..	...	...	...	...	..	...	..	...	...	...	2	50	14	86		
Eyermann	91	97	52	90	4	100	...	...	..	...	14	36	6	17	...	...	14	93		
Friedlaender and Feinberg	83	83	...	..	...	...	19*	11	..	...	..	...	16*	0	9	78	14	71	13	85
Koelsche	83	102	71	71	...	...	...	...	19	47	..	...	12	33						
Levin	223	223	78	59	...	...	14*	29	..	...	..	...	87†	66	2	100	9	67	10	60
Logan	18	21	12	83	...	...	2	100	3	67	..	...	1	100	...	...	1	100		
Loveless	51	53	38	82	2	100	...	...	1	100	1	0	2	0	2	100	1	100	2	0
McElin and Horton	81	81	22	95	...	...	8	88	..	...	..	...	3†	33	4	100				
O'Leary and Farber	236	236	...	..	...	...	...	...	..	...	..	...	...	...	50	92	110	88	25	35
Shaffer	13	13	...	..	...	...	...	...	..	...	..	...	...	...	4	100	4	100	3	66
Thacker	72	80	...	..	...	...	70*	46	..	...	8	50								
Todd	188	188	11	100	...	...	35	100	..	...	..	...	24*	79	35	100	43	100		
Waldbott	165	165	31	74	...	...	23	74	30	47	..	...	48*	50	...	...	20‡	80	6	33
Williams	23	23	...	..	...	...	12*	83												
Gastineau, Harley, Pinkus, Notier and Epstein	43	43	5	80	...	...	...	...	..	...	..	...	11*	45	9	100	2	100	11	82
Total	1453	1493	320	..	6	...	183	...	53	...	23	...	210	...	135	...	261	...	76	
Average per cent	....	....	...	77	...	100	...	60	...	49	..	39	...	53	...	95	...	87	..	58

* Non-seasonal—not specified as to whether intrinsic or extrinsic.
† Not classified as to intrinsic or extrinsic but "mixed" (some infectious).
‡ Urticaria only.

TABLE IB

CLINICAL EFFECTIVENESS OF HISTAMINE ANTAGONISTS IN MISCELLANEOUS DISORDERS: BENADRYL

Investigator	Dermatitis				Dermographism		Physical Allergy		Pruritus		Serum Disease		Migraine		Ménière's Syndrome		Headache		Miscellaneous	
	Contact		Miscellaneous																	
	No. Complaints	No. Improved %	No. Complaints	No. Improved %	No. Complaints	No. Improved %	No. Complaints	No. Improved %	No. Complaints	No. Improved %	No. Complaints	No. Improved %	No. Complaints	No. Improved %	No. Complaints	No. Improved %	No. Complaints	No. Improved %	No. Complaints	No. Improved %
Bowen	5	100	..	...	1	100	..	...	..	...	1	100	3	0	1	100	1	0		
Curtis, Owens	..	...	..	...	2	100	1	0	1	100	..	...	1	0	..	...	..	..	6	0
Eyermann																				
Friedlaender and Feinberg	3	100	1	100	3	100	4	75	1	100										
Koelsche																				
Levin	3	67	2	50	..	...	..	...	..	...	..	...	18	61						
Logan	..	...	..	...	..	...	..	...	..	...	1	100	..	..	..	...	..	..	1	0
Loveless	..	...	..	...	..	...	..	...	..	...	..	...	..	..	..	...	..	..	4	100
McElin and Horton	2	0	2	0	..	...	1	100	..	...	..	...	4	25	6	50	13	69	16	6
O'Leary and Farber	..	...	..	...	..	...	..	...	38	16	..	...	..	..	..	...	..	..	13	85
Shaffer	..	...	2	50																
Thacker	..	...	..	...	..	...	..	...	..	...	..	...	..	..	2	50				
Todd	5	80	12	83	..	...	..	...	..	...	1	100	8	38	2	100	..	..	12	100
Waldbott	..	...	..	...	..	...	..	...	..	...	..	...	4	50	..	...	..	..	3	100
Williams	..	...	..	...	..	...	..	...	..	...	..	...	..	..	2	100	..	..	9	100
Gastineau, Harley Pinkus, Notier and Epstein	..	...	4	100	..	...	1	100												
Total	18	...	23	...	6	...	7	...	40	...	3	...	38	..	13	...	14	..	64	
Average per cent	..	78	..	74	..	100	..	71	..	20	..	100	..	45	..	69	..	64	..	63

TABLE IIA

CLINICAL EFFECTIVENESS OF HISTAMINE ANTAGONISTS IN ALLERGIC DISORDERS: PYRIBENZAMINE

Investigator	Total Number of Patients	Total Number of Complaints	Allergic rhinitis						Bronchial asthma						Urticaria				Dermatitis	
			Extrinsic				Intrinsic		Extrinsic				Intrinsic		Acute		Chronic		Atopic	
			Seasonal		Non-seasonal				Seasonal		Non-seasonal									
			No. Complaints	No. Improved %	No. Complaints	No. Improved %	No. Complaints	No. Improved %	No. Complaints	No. Improved %	No. Complaints	No. Improved %	No. Complaints	No. Improved %	No. Complaints	No. Improved %	No. Complaints	No. Improved %	No. Complaints	No. Improved %
American Acadamy of Allergy	978	978	104	54	...	..	277*	59	11	45	..	..	211*	31	121	78	97	78	59	51
Arbesman	495	576	140	85	138	72	35	48	30	48	62	45	6	17	47‡	94	101	78	(several	100)
Epstein	22	22	...	..	...	..	...	...	..	..	..	..	...	..	9	100	6	83	7	100
Feinberg and Friedlaender	503	503	254	83	...	..	85	59	..	..	..	..	70*	34	18	89	27	78	20	80
Loveless	127	151	60	85	6	67	2	100	1	0	8	75	7	43	31†	84	12	50	3	33
Osborne	83	83	...	..	...	..	...	...	..	..	..	..	...	..	24	96	23	39	30	63
Total	2208	2313	558	..	144	..	399	...	42	..	70	..	294	..	250	...	266	..	119	
Average per cent	....	....	...	78	...	72	...	58	..	45	..	49	...	32	...	85	...	79	...	61

* Not specified as to whether of extrinsic or of intrinsic origin.

† Twenty-seven patients with drug hypersensitivity responded in 89 per cent of the instances; others not hypersensitive to drugs were relieved in 50 per cent of instances.

‡ Eleven patients with drug hypersensitivity responded in 100 per cent of the instances, others not hypersensitive to drugs were relieved in 92 per cent of thirty-six instances.

TABLE IIB

CLINICAL EFFECTIVENESS OF HISTAMINE ANTAGONISTS IN MISCELLANEOUS DISORDERS: PYRIBENZAMINE

Investigator	Dermatitis		Dermographism		Physical Allergy		Pruritus		Serum Disease		Migraine		Ménière's Syndrome		"Constitutional" Reaction		Headache		Miscellaneous	
	Non-Atopic																			
	No. Complaints	No. Improved %	No. Complaints	No Improved %	No. Complaints	No. Improved %	No. Complaints	No. Improved %	No. Complaints	No. Improved %	No. Complaints	No. Improved %	No. Complaints	No. Improved %	No. Complaints	No. Improved %	No. Complaints	No. Improved %	No. Complaints	No. Improved %
American Academy of Allergy..	22	32	23	78	5	40	21	57	..	..	6	17	5	20	..	...	5	60	11	27
Arbesman ...	..	..	6	83	3	100	..	...	..	...	..	..	..	..	8	100	..	..	..	..
Epstein.....	..	..	..	...	..	...	..	...	..	...	..	..	..	..	..	...	..	..	..	..
Feinberg and Friedlaender....	5	80	16	88	..	..	3	100	..	...	..	..	..	..	..	...	3	33	2	50
Loveless.....	..	..	1	100	..	..	2	50	1	100	..	..	..	..	17	88	..	..	..	..
Osborne.....	4	75	..	..	2	100	..	...	..	...	..	..	..	..	..	...	..	..	..	..
Total.....	31	..	46	...	10	...	26	...	1	...	6	..	5	..	25	...	8	..	13	
Average per cent...	..	45	..	83	..	70	..	61	..	100	..	17	..	20	..	92	..	50	..	31

ous types responded in over three-fourths of the trials with benadryl. A comparison with the related data for pyribenzamine (PBZ) showed little difference in the efficiency of the two drugs. No comparison was possible, however, in the instance of contact type of eczematous dermatitis since there are no reports on the use of PBZ for this condition. Whereas benadryl benefited the majority of patients with physical allergy, Ménière's syndrome, certain cephalalgias, intrinsic allergic rhinitis and atopic dermatitis, the results were less encouraging with asthma, migraine and pruritus.

The therapeutic results obtained with benadryl and PBZ will now be briefly discussed.

Serum Disease. Four observers each reported symptomatic relief of serum disease in a single patient. (Table III.) The patient given PBZ was in the author's series. She was a young woman who had received a prophylactic inoculation of tetanus antiserum and who developed generalized urticaria within two hours, with subsequent hypotension of critical degree and lapses of consciousness. Once 50 mg. doses of PBZ had been instituted by mouth it was possible to discontinue the frequent injections of epinephrine needed to maintain the arterial tension. The intense pruritus and urticarial eruption were also controlled. After four hourly doses no further treatment was required.

Constitutional Reactions Following Overdosage with Allergenic Solutions. Four cases listed under benadryl and seventeen of the twenty-five patients given PBZ were in the writer's series. The only failures observed were among patients who developed rather marked bronchospasm as part of their "constitutional" response to injected allergen, two of four such patients showing no improvement within thirty minutes after taking 50 mg. of PBZ. All others responded to their accidental overdosage with pollen extract by developing signs of hay fever, urticaria and occasionally a mild cough or dyspnea. These symptoms and signs yielded uniformly, although not always completely, to one 50 mg. dose of the selected histamine antagonist within twenty or thirty minutes.

TABLE III

DISORDERS ALLEVIATED BY HISTAMINE ANTAGONISTS IN ORDER OF THEIR SUSCEPTIBILITY TO BENADRYL AND IN COMPARISON WITH PYRIBENZAMINE

	Benadryl		Pyribenzamine	
	Patients Treated	Number Improved, %	Patients Treated	Number Improved %
Serum disease	3	100	1	100
Overdose reactions	4	100	25	92
Dermographia	6	100	46	83
Allergic rhinitis, extrinsic non-seasonal	6	100	144	72
Urticaria, acute	135	95	250	85
Urticaria, chronic	261	87	266	79
Dermatitis, contact	18	78		
Rhinitis, seasonal (hay fever)	320	77	558	78
Dermatitis, eczematous and miscellaneous	23	74†	31	45
Physical allergy	7	71	10	70
Ménière's syndrome	13	69†	5	20
Headache, histamine and other types	14	64	8	50
Rhinitis, intrinsic* allergic	183	59	399	58
Dermatitis, atopic	76	58	119	61
Asthma, intrinsic* allergic	210	53†	294	32
Asthma, seasonal	53	49	42	45
Migraine	38	45	6	17
Asthma, non-seasonal extrinsic	23	39	70	49†
Pruritus	40	20	26	61

* Some of the diagnostic data were inadequate to determine whether the patient belonged to the intrinsic or to the non-seasonal extrinsic class.

† Suggested superiority over the other drug.

With the exception of the two patients who required the use of epinephrine, no other therapy was used for the overdose reactions.

The remaining eight trials were carried out by Arbesman in a somewhat different manner. Having noted an untoward response in a given individual after a certain dose of allergen, he then prevented a reaction during the next visit by giving 100 mg. of PBZ twenty minutes beforehand. At the following visit the same amount of therapeutic solution was once more inoculated, with recurrence of the untoward response.

The possibilities of the antihistaminic agents as aids to the management of unduly

sensitive patients and to the shortening of "booster" courses should be more fully explored. Large numbers of observations will be needed in order to minimize the factor of variability in a given patient's handling of a selected dose and to exclude the possibility that the drugs might postpone, rather than avert, the undesirable reaction. It is obvious that the histamine antagonists will prove unsuitable for the relief of serious systemic manifestations if employed by mouth, since too long a time is required for their absorption.

Dermographism. This appears to be a good prospect for therapy with the new drugs. In our single experience both the flare and the wheal with its associated pruritus were decidedly reduced by 50 mg. of PBZ taken twenty minutes before the fingerstroke of the skin. Baer and Sulzberger[26] have described a similar experiment. The data on benadryl are few.

Vasomotor Rhinitis, Extrinsic Nonseasonal. An example of this disturbance is the perennial nasal and conjunctival allergic state caused by sensitivity to housedust or animal emanations. The finding that benadryl controlled this type of complaint uniformly, whereas PBZ benefited only three-fourths of the subjects, is no doubt due to inadequate sampling in the former group.

Urticaria. Urticaria was classified as acute if it had been present for three weeks or less. It yielded in a high proportion of some 400 tests with the two drugs. Many of these eruptions had been provoked by chemotherapy, especially with penicillin. The difference noted in the efficiency of the two drugs is probably not of statistical significance, especially since most observers dealt with one agent only. If additional trials indicate that benadryl is superior to PBZ, this may be explained by the greater sedative effect of the former and the well known beneficial influence of sedation upon pruritus.

Chronic urticaria has been thoroughly tested with the two new drugs. The average attack was definitely improved, at least subjectively, by either agent. Considering the therapeutic problems these patients have presented in the past, a positive result in some 80 per cent of all trials is most heartening.

Contact Type of Eczematous Dermatitis. The pruritus, but usually not the lesion of poison ivy and similar eruptions, yielded to benadryl in three-fourths of the eighteen patients treated. Observations on the effect of PBZ are lacking.

Hay Fever. Nearly 80 per cent of the 800 individuals, who were given one or another of the histamine antagonists when they were having seasonal allergic rhinitis, experienced decided relief within half an hour after an oral dose of 50 mg. The agents appear to be of equal efficacy and of real value for this disorder.

Dermatitis, Eczematous and Miscellaneous. That this group covers a heterogeneous assortment of non-atopic eruptions will be apparent from the following facts. The single case listed for Friedlaender and Feinberg in Table IB was described by them as an unclassified dermatitis. The two patients given benadryl by Levin were sulfonamide-sensitive, one of McElin's subjects had psoriasis and another had orthostatic purpura, Shaffer reported one trial with lichen urticatus and another with recurrent dyshidrotic eczema, Todd observed twelve patients with eczematoid dermatitis and Pinkus experimented with four individuals who had erythema exudativum multiforme. Seventeen, or 74 per cent, of these patients with hetereogeneous disorders responded favorably to benadryl.

The data for PBZ are equally disseminated from the diagnostic viewpoint. The contributors to the report of the American Academy of Allergy listed nine of their trials under the incomplete heading, "eczema,"

five more under the heading, "eczematous dermatitis," seven under "unclassified dermatitis" and one under "drug rash." Of these 22 patients, seven or 32 per cent were improved by pyribenzamine. Feinberg and Friedlaender found that four of their five subjects with unclassified dermatitis were relieved by the drug, as were three of Osborne's four patients with drug eruptions caused by sulfonamides and barbiturates.

It is obvious that more studies will have to be carried out with the various types of non-atopic dermatitis and that more complete information will be needed as to the diagnosis and the degree of relief attained.

Atopic Dermatitis. This was typified by infantile eczema. It was well defined by all observers and an adequate number of patients were involved (nearly 200) to permit of reliable conclusions. Approximately 60 per cent of all trials with either drug brought appreciable relief. However, this was usually of subjective rather than of an objective nature. It will be interesting to learn whether significant sampling of other types of dermatitis will lead to a shift in their positions on the table of susceptibility to the new drugs. The limited data available at this writing place contact and other non-atopic types of dermatitis in the near vicinity of hay fever, an atopic disorder. Atopic dermatitis, on the other hand, falls seven places further down the susceptibility list.

Physical Allergy, Ménière's Syndrome and Headache. Since 70 per cent of trials with the drugs brought more or less relief to patients diagnosed as hypersensitive to cold or heat, it will be profitable to accumulate more experience along this line. The trials with histamine antagonists in Ménière's syndrome are likewise limited in number but encouraging, especially in the instance of benadryl. It will be particularly interesting if the success of the Mayo group with histamine and tension headaches can be substantiated by additional tests. (McElin, Table IB.)

Intrinsic Allergic Rhinitis. This is a chronic nasal condition characterized by obstruction, watery coryza and sneezing. It is thought to be due to "bacterial allergy" or other inherent factors, rather than to extrinsic allergens which can be determined by a case history and allergic tests. This obscure disorder was responsive, at least partially, in 60 per cent of the 582 trials made with either drug. Since such patients are always therapeutic problems any symptomatic aid will be welcomed.

It should be stated at this point that considerable ambiguity was encountered in the published reports on this group. Indeed, part of the data placed under our heading, "intrinsic" rhinitis may belong under the classification of "extrinsic, nonseasonal" rhinitis. This situation arose because most observers described their patients as having nonseasonal nasal symptoms, without stipulating whether the cause was extrinsic or intrinsic. Transfer of all such data, marked by footnotes in Tables IA and IIA, to the extrinsic column would lower the average for the extrinsic class to 45 per cent in the case of benadryl and to 64 per cent in the instance of PBZ. The figure for the intrinsic groups would conversely be heightened to 90 per cent for benadryl and remain approximately as before for PBZ.

Until future reports clarify the situation, it will probably simplify matters to divide allergic rhinitides into two large classes: the first to contain all cases of known extrinsic origin, whether of seasonal or non-seasonal occurrence, and the second to cover all other varieties. When the data of Tables I and II are combined in this manner, 77 per cent of all trials with either drug for the extrinsic forms gave a positive response. This figure is the same as that found for the seasonal variety alone, which suggests that our classification of doubtful cases (as

intrinsic) was probably correct. It seems probable, therefore, that additional observations upon the intrinsic type will show them to be relatively refractory to the histamine antagonists.

Bronchial Asthma. Bronchial asthma, like vasomotor rhinitis, was difficult to evaluate for the reason that it too was frequently classified incompletely by those experimenting with PBZ and benadryl. Some described their cases merely as those of "asthma" or "non-seasonal asthma," without reference to etiology. These have been indicated by asterisk and footnotes in Tables I and II. They account for 189 of the trials with benadryl listed by us arbitrarily under the heading, "intrinsic asthma" and their removal would leave only twenty-one patients with clearly labelled intrinsic etiology. The latter responded to benadryl in only 29 per cent of the tests. Similar exclusion of doubtful data from the PBZ analysis reduces the number of intrinsic cases to thirteen and the incidence of relief to 31 per cent.

The shift of these doubtful cases into the "extrinsic, non-seasonal" asthmatic class brings the average figure for relief from benadryl up by about 15 per cent (to 54 per cent) and that of the PBZ series down about 15 per cent (to 35 per cent). Our inability to decide in which category the doubtful data belong is perhaps of no great importance, because the result does not differ materially in either analysis from that found for the readily diagnosed seasonal variety of asthma. These extrinsic types were relieved by benadryl in 49 per cent of the trials and by PBZ in 45 per cent. It seems probable that clearly established cases of the intrinsic form will be found even less amenable to antihistaminic agents. At any rate, the present survey indicates that all allergic kinds of asthma yield rather poorly to benadryl and to PBZ, since they will be seen to fall in the lower third of the nineteen disorders named in Table III. Nevertheless, the need is so great for agents which will relieve asthma without the involvement of the hypodermic syringe or complicated inhalation apparatus that any addition to our armamentarium should be welcomed.

Migraine. Migraine was treated with benadryl by six investigators, with at least partial relief for the patient in 45 per cent of the thirty-eight trials. Only six patients were given PBZ and all but one proved resistant. The possibility that so simple a therapy might be effective for this dreaded complaint makes it urgent that further trials be reported.

Pruritus. Pruritus was little affected by benadryl but rather well controlled by PBZ in a limited experience. O'Leary employed the former for the itching of contact dermatitis, of jaundice, psoriasis, dermatitis herpetiformis and pruritus of neurogenic or toxic origin. No information is available as to the type of patient given PBZ by the American Academy of Allergy group. Further observations will no doubt be forthcoming in the future, since any hope of combatting this most disturbing of conditions ought to be diligently pursued.

Miscellaneous. Encouraging results were reported in limited experiments with such disorders as allergic laryngitis, allergic conjunctivitis, hyperplastic ethmoiditis, overdose reactions and food allergy.

SIDE REACTIONS

Two reports on PBZ and six on benadryl included data on side effects which have been added to our own for analysis of incidence and types.

Table IV shows that 23 per cent of the 1,905 individuals given PBZ developed undesirable reactions. The comparable figure for 655 trials with benadryl was 61 per cent—nearly threefold that of the other drug.

The nature of the side effect and the

TABLE IV

SIDE REACTIONS OF HISTAMINE ANTAGONISTS (PYRIBENZAMINE AND BENADRYL)

Investigator	Incidence of Side Effects				Distribution of Side Reactions																				Total Number of Side Reactions	
	Total Number of Patients Observed		Per Cent with Side Reactions		Drowsiness		Gastro-intestinal		Headache		Vascular		Allergy		Nervous		Numbness of Lips and Tongue		Exhaustion		Dizziness		Muscle Incoordination		Miscellaneous			
	PBZ	Bena.	PBZ %	Bena. %	PBZ %	Bena. %	PBZ %	Bena. %	PBZ %	Bena. %	PBZ %	Bena. %	PBZ %	Bena. %	PBZ %	Bena. %	PBZ %	Bena. %	PBZ %	Bena. %	PBZ %	Bena. %	PBZ %	Bena. %	PBZ %	Bena. %	PBZ	Bena.
American Academy of Allergy	978	...	17	..	6	..	4	..	1	..	0.5	..	0.1	..	2	..	0.7	....	0.1	...	2	..	...	....	0.1	...	168	
Arbesman*	800	...	27	..	9	..	15	..	4	..	2	..	2	..	4	..	2	....	5	...	4	..	...	....	0.5	...	376	
Curtis and Owens	....	18	..	17	....	11	..	..	...	..	...	..	...	..	..	..	...	....	...	6	..	6	...	11	...	...	...	6
Eyermann	....	52	..	38	....	25	..	12	...	..	...	..	...	..	..	21	...	....	...	6	..	10	...	....	...	...	...	38
Levin*	....	223	..	65	....	38	..	9	...	..	...	8	...	2	..	14	...	3	...	5	..	9	...	....	...	...	...	191
Loveless	127	51	40	71	23	61	14	10	2	..	1	..	1	2	4	6	2	2	3	10	3	6	2	4	1	2	70	52
McElin and Horton	....	74	..	73	....	59	..	14	...	..	...	3	...	..	..	22	...	15	...	8	..	16	...	4	...	...	...	104
Thacker	....	72	..	67	....	39	..	8	...	..	...	..	...	..	..	11	...	25	...	7	..	7	...	....	...	...	...	70
Waldbott	....	165	..	56	....	49	..	3	...	..	...	..	...	2	..	..	...	0.6	...	...	..	..	...	1	...	...	...	92
Total	1905	655	..	..	....	..	..	..	...	..	...	..	...	..	..	..	...	....	...	...	..	..	...	....	...	...	614	553
Average per cent	....	...	23	61	8½	43	9	8	2½	0	1	3	1	1	3	10	1	6	2	4.6	3	7	0.1	1.4	0.3	0.2		

* Personal communication as well as the published article.

frequency of its appearance are listed for each investigator in Table IV. From this it was possible to list the various manifestations in order of their prevalence with relation to either drug. (Table V.)

The side reaction most commonly encountered after the administration of benadryl was sedation. It took the form of drowsiness, inability to concentrate, mental confusion, prolonged and untimely sleep, stupor and narcolepsy. These were noted five times more often after the administration of benadryl than following PBZ. Among our own patients the ratio was approximately three to one.

TABLE V
SIDE REACTIONS OF BENADRYL AND PYRIBENZAMINE IN ORDER OF THEIR FREQUENCY

Benadryl		Pyribenzamine	
Side Effect	Incidence %	Side Effect	Incidence %
Sedation	43	Gastrointestinal	9
Central or peripheral nervous system	10	Sedation	8½
Gastrointestinal	8	Central or peripheral nervous system	3
Dizziness or vertigo	7	Dizziness or vertigo	3
Numbness of lips and tongue	6	Headache	2½
Exhaustion	4½	Exhaustion	2
Vascular	3	Numbness of lips and tongue	1
Muscular pain or incoordination	1½	Vascular	1
Hypersensitiveness	1	Hypersensitiveness	1
Miscellaneous	0.2	Miscellaneous	0.3
Headache	0	Muscular pain or incoordination	0.1

In the instance of PBZ, the most common side effects were in the gastrointestinal tract as evidenced by such complaints as nausea, "bad taste" in the mouth, anorexia, heartburn, epigastric distress, indigestion, abdominal cramps and occasionally vomiting and diarrhea. The second most common side response to benadryl was one of apparent irritation of the central or peripheral nervous system which led patients to report such states as "wakeful excitement," "jitters," insomnia, irritability, nervous tension, somnambulism, "chills," palpitations, blurring of the vision, diplopia, exuberance, numbness of the extremities, olfactory hallucination (smell of paraldehyde), dryness of the nasal membranes and such urinary disturbances as dysuria, polyuria and frequency. They were encountered in 10 per cent of the trials with benadryl, whereas only 3 per cent of patients given PBZ described such conditions.

Gastrointestinal disturbances were next in order of frequency after the administration of benadryl, being noted in 8 per cent of the patients. Approximately the same proportion of those taking PBZ reported this type of side effect.

Dizziness and vertigo were rather common complications of either drug, being present in 7 per cent of the trials with benadryl and 1 per cent of the PBZ series. Numbness of the lips and tongue occurred in 6 per cent of the tests with benadryl but in only 1 per cent of those with PBZ. It was referable no doubt to local anesthetic action.

Exhaustion (which perhaps should have been included in our sedation class) followed 4½ per cent of the treatments with benadryl and 2 per cent of those with PBZ, ranking sixth in order of frequency for either drug. The next group was comprised of such conditions as flushing of the skin, tachycardia, "tendency to bleed," perspiration, coldness of the extremities, pallor, facial edema, tinnitus and collapse. These were put together under our heading of "vascular." They were present in 3 per cent of those taking benadryl and in 1 per cent of the patients given PBZ.

Such symptoms as tenderness or aching of the muscles, twitchings and impaired

coordination of the extra-orbital muscles were rarely encountered, the incidence being 1½ per cent for benadryl and 1/10 of 1 per cent for PBZ. The latter was accounted for by two of our patients, one of whom developed diplopia for a short time and another who transiently found great difficulty in lifting small objects for an hour after PBZ had been absorbed.

During the course of therapy, a small percentage (about 1 per cent) of patients given either antihistamine developed what appeared to be hypersensitiveness toward the pill or capsule. For example, the writer observed one individual whose cough was aggravated by PBZ and Arbesman described nineteen who showed an increase in the original complaint during treatment.

Under the heading, "miscellaneous," we included a patient with early menstruation, two instances of impotence, two of menorrhagia and one of emotional depression following the ingestion of PBZ. Only one item was placed in this category for benadryl and it consisted of a feeling of depressed spirits in one of our subjects.

It is interesting that no instance of headache was found among the side effects of benadryl, whereas this was the fifth most common reaction to PBZ, being noted in 2½ per cent of all patients given this drug.

Most of the side reactions discussed above were of mild intensity, requiring no treatment other than discontinuance of antihistaminic therapy. It is the writer's impression that the incidence and severity of side effects can be reduced by the simple precaution of prescribing food or sugar to be taken with the drugs and also by the use of some mild stimulant, such as caffeine or benzedrine, to negate sedation.

SUMMARY AND CONCLUSIONS

This survey of the clinical experience with benadryl and pyribenzamine makes it clear that these drugs confer excellent symptomatic relief in urticaria, especially the acute form due to chemotherapeutic agents. Hay fever and other allergic rhinitides of extrinsic (or determinable) origin also yield well, although less spectacularly, to the usual 50 or 100 mg. doses of either drug, whereas cases classed as intrinsic or infectious appear to be less amenable. Atopic dermatitis was improved, at least subjectively, in more than half the reported trials with either drug. Although asthma of all allergic types appears to be less susceptible to the new agents than are other atopic disorders, future observations on well differentiated cases may reveal that a difference exists between the intrinsic and the extrinsic forms as far as their susceptibility to histamine antagonists is concerned.

A number of disorders offer great promise as candidates for this type of symptomatic treatment but observations on them to date are too limited for conclusions. These include serum disease, constitutional reactions due to overdosage with allergenic solutions, dermographism, and to a lesser extent, contact and other types of nonatopic dermatitis, physical allergies, Ménière's syndrome, histamine headache and migraine. Further data should also clarify the usefulness of histamine antagonists in pruritus of various origins.

Side reactions are nearly three times as frequent after benadryl as they are following PBZ. Sedation was noted in 43 per cent of those given benadryl and 8½ per cent of the PBZ group. Whereas this effect was the most common untoward manifestation after benadryl was given, gastrointestinal disturbances ranked first after the administration of PBZ. Other frequently observed side effects with either drug were assumed to be related to central stimulation, since those affected experienced insomnia, nervous tension, restlessness, etc. Dizziness and vertigo held the fourth place for each drug and numbness of the lips and tongue as

well as a sense of generalized exhaustion were relatively common complaints. Infrequently reported were vascular disturbances (flushing, tachycardia, pallor, etc.), muscular pains and incoördination, headache (occurring only after the administration of pyribenzamine), allergy to the drug and rarely, impotence or disorders of menstruation.

More investigations are needed to determine the sites of action of these new pharmaceutical agents and additional clinical trials are in order to establish their full therapeutic range.

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Evaluation of Dimethylaminoethyl Benzhydryl Ether Hydrochloride (Benadryl) in Bronchial Asthma*

ABNER M. FUCHS, M.D., PHILIP M. SCHULMAN, M.D. *and*
THOMAS H. MCGAVACK, M.D.
NEW YORK, NEW YORK

In recent years there has been an attempt to produce drugs which would be effective for the relief and prevention of various allergic manifestations. Since it is generally believed that at least some of the symptoms occurring in allergic diseases are due to the liberation of histamine or a histamine-like substance, several chemical compounds have been synthesized in an attempt to block the action of histamine. One of these drugs, dimethylaminoethyl benzhydryl ether hydrochloride, commonly known as benadryl, has been shown to possess high anti-histaminic properties. Animal experimentation has shown that this drug is a powerful antagonist to many of the pharmacological actions of histamine.[1] It was shown to be very effective in relieving anaphylactic shock in guinea pigs and in preventing death from bronchospasm following fatal doses of histamine.[2]

Clinical reports on the therapeutic effects of benadryl have been favorable when employed in such conditions as urticaria and angioneurotic edema.[3,4] It seems to be of value in serum sickness and in relieving itching in various types of dermatitis.[5] When administered orally in sufficient amounts the drug is capable of diminishing the reaction of the skin to histamine.[6] The reports thus far on its[7–15] value in bronchial asthma have been inconclusive.

In an effort to determine the value, if any, of benadryl* in the treatment of bronchial asthma, the drug was administered to a group of thirty adult asthmatics who have been attending the Allergy Clinic of the Metropolitan Hospital for many years, and who were resistant to all forms of the usual asthmatic remedies such as elimination of substances giving positive skin reactions, dust and pollen immunization, catarrhal vaccine, and anti-asthmatic drugs commonly employed for symptomatic relief. (Table 1.) The patients' ages ranged from twenty to eighty years and the duration of the asthmatic symptoms was from two to forty years. Twenty-eight of them had complicating organic disease of the sinuses, lungs or heart as demonstrated by *x*-ray or electrocardiographic examination. Eleven of the patients belonged to the skin negative or infective group, in whom sensitization to specific allergens such as pollens, inhalants and foods was not demonstrated by skin tests or clinical trial. Their symptoms were the result of some infectious process in the paranasal sinuses, lungs or elsewhere in the body. The remainder, or nineteen of the patients, were of the mixed type in that they were skin sensitive and also had chronic

* Generous supplies of benadryl have been made available through the courtesy of Dr. E. A. Sharp, of Parke, Davis & Co., Detroit, Mich.

* From the Allergy Clinic, Department of Medicine, Metropolitan Hospital and the New York Medical College, Metropolitan Hospital Research Unit, Welfare Island, New York City.

TABLE I

CLINICAL DATA IN THIRTY CASES OF BRONCHIAL ASTHMA IN WHICH BENADRYL WAS USED

No.	Case	Age	Duration of Asthma	Type			Frequency of Attacks	Dosage of Benadryl	Clinical Impression			Vital Capacity before and after Benadryl		Side Effects				Complications	Specific Treatment
				All.	Inf.	M.			CR.	I.	U.	Before	After	Drowsiness	Dizziness	Dry Mouth	Fatigue		
1	A. T.	60	8 years		I		Daily	150–300 mg.			U	1.4	1.2	xx	x	..	..	Chronic bronchitis with emphysema	D V
2	L. D.	51	12 years			M	Daily	150–300 mg.			U	2.2	1.2	xx	x	xxx	..	Sinusitis	D V
3	F. R.	48	8 years			M	Daily	150–300 mg.		I		2.3	2.5	xx	xx	..	..	Hypothyroidism, obesity	D Thyroid ext.
4	E. O.	75	32 years			M	Seasonal	100–300 mg.		I		2.0	3.0	xx	x	..	..	Ragweed pollinosis, pulmonary tuberculosis (healed)	D V
5	J. T.	80	7 years		I		Seasonal	150–300 mg.		I		2.0	2.6	xx	..	..	..	Generalized arteriosclerosis, parkinsonism	D V
6	J. P.	40	10 years		I		Perennial	150 mg.			U	2.9	3.2	xxx	xxx	..	xxx	Sinusitis. Patient refused to continue with benadryl because of severe reactions	
7	J. S.	58	12 years		I		Daily	150–300 mg.			U	1.0	1.2	xx	x	..	..		V
8	E. P.	57	27 years			M	Daily	150–300 mg.			U	1.4	1.4	xxxx	xx	..	xx	Coronary sclerosis, emphysema	D
9	C. W.	54	8 years		I		Seasonal	150–300 mg.		I		1.8	1.6	xx	x	..	..		V
10	A. C.	45	25 years			M	Daily	100–200 mg.			U	2.7	2.8	xxx	xxx	xx	xxx	Patient refused to continue with benadryl because of severe side effects; sinusitis	D V
11	A. S.	63	15 years			M	Daily	150–300 mg.			U	1.3	1.2	xx	xx	..	..	Pulmonary tuberculosis (active?)	V
12	P. L.	40	6 years		I		Daily	150–300 mg.			U	1.6	2.3	xxx	xx	..	..	Chronic bronchitis with emphysema; bronchiectasia	KI V
13	T. G.	50	3 years		I		Perennial	150–250 mg.			U			xx	xx	..	x	Discontinued benadryl because of drowsiness; sinusitis	D V KI
14	J. Z.	29	2 years			M	Seasonal	150–200 mg.			U			xx	x	..	..	Neurodermatitis, sinusitis; discontinued benadryl because of drowsiness	
15	D. R.	48	12 years			M	Perennial	150 mg.			U	1.3	2.3	xx	xx	..	..	Status asthmaticus, pansinusitis	D V
16	J. P.	68	40 years		I		Perennial	150–200 mg.			U	2.7	2.8	..	..	..	..	Arteriosclerotic heart disease, auricullar fibrillation, emphysema	D V KI
17	L. G.	20	9 years			M	Perennial	150–200 mg.		I		1.8	3.0	xx	xx	..	..	Sinusitis	KI V
18	R. P.	61	7 years			M	Perennial	150–300 mg.			U	2.2	2.5	xx	..	..	..	Arteriosclerotic heart disease, cardiac decompensation, coronary sclerosis	D V KI
19	N. D.	65	15 years			M	Daily	150–300 mg.			U	1.7	2.1	xxx	xx	x	..	Coronary sclerosis, angina pectoris, bundle branch block	V
20	E. W.	46	35 years			M	Perennial	150–300 mg.			U	3.2	3.4	xx	..	..	..	Chronic bronchitis, syphilis	D KI
21	F. C.	36	8 years			M	Perennial	100–200 mg.		I				x	..	..	..	Sinusitis	D
22	B. F.	28	10 years		I		Daily	100–300 mg.			U			xxxx	xxxx	..	..	Chronic bronchitis with emphysema; neurodermatitis	D V KI
23	B. M.	46	4 years			M	Seasonal	100–150 mg.			U			xxxx	..	..	..	Sinusitis; patient discontinued benadryl because of severe side effects	
24	J. M.	47	4 years			M	Seasonal	100–200 mg.			U			xxx	xx	..	..	Pollinosis, sinusitis, bronchitis	D KI
25	F. G.	42	5 years		I		Daily	150–400 mg.			U			xx	xxxx	..	..	Discontinued benadryl because of severe side effects, pansinusitis, emphysema	D V
26	B. R.	21	17 years			M	Perennial	150–400 mg.			U			xxxx	xx	..	..	Sinusitis, bronchiectasis, pollinosis	D V T. O. & R Alt. & Horm.
27	H. W.	27	14 years			M	Perennial	150–400 mg.			U			xxxx	xx	..	..	Sinusitis, emphysema, pollinosis	D V T. O. & R.
28	M. B.	44	11 years			M	Daily	150–400 mg.			U			xx	xxxx	..	..	Pollinosis, sinusitis, bronchiectasis. Discontinued benadryl, severe side effects	D V T. O. & R
29	A. G.	68	2 years		I		Daily	150–400 mg.			U			xxx	xxxx	..	..	Chronic bronchitis with emphysema; arteriosclerotic heart disease	D V KI
30	B. E.	47	25 years			M	Perennial	150–200 mg.		I				xx	xx	..	..	Pollinosis, sinusitis	T. O. & R.

All.—Allergic
Inf.—Infectious
M.—Mixed
CR.—Complete Relief

I—Improved
U—Unimproved
Spirometer studies were done with a Collins Spirometer and measurements were made in liters per square meter of body surface

D—Dust extract
V—Vaccine
KI—Potassium iodide
T—Timothy grass pollen
O—Orchard grass pollen
R—Ragweed pollen
Alt.—Alternaria
Horm.—Hormodendron

infections. None of the patients could be classified as solely of the skin sensitive type.

All of the patients were at first given 150 mg. of benadryl daily. They were instructed to take 1 tablet (50 mg.) by mouth three times a day after meals. When no relief was obtained after two week's trial, the quantity was gradually increased in an effort to determine the patient's daily requirements. An additional 100 mg. was prescribed at bedtime. If no improvement followed, the dosage was increased further to 300 to 400 mg. per day (100 mg. three times a day after meals and sometimes an additional 100 mg. at bedtime). The patients were observed for a period of six months and were required to keep daily records of their symptoms. Once a week the results were recorded as symptoms completely relieved, improved or unimproved. When the improvement persisted for a period of four weeks on benadryl medication a placebo was substituted for a period of two weeks. Immunization treatment with pollen extract, dust extract or catarrhal vaccine was continued. All anti-asthmatic drugs except benadryl were discontinued but when benadryl was shown to be ineffective such medications as ephedrine, potassium iodide or aminophyllin were used in conjunction with benadryl. Pulse studies were made on all of the patients. Spirometer determinations were made on eighteen patients before and after taking benadryl using the Collins respirometer; measurements are recorded in liters per square meter of body surface.

RESULTS OF TREATMENT

Seven of thirty patients or 23 per cent treated with benadryl reported symptomatic relief. It is of interest to note that these patients showed no evidence of organic lung or heart disease except Case 4 whose *x*-ray revealed some healed tuberculous scars. Furthermore, episodes of acute respiratory infections were conspicuously absent in these patients during the six-month period of observation. Two of these patients (Cases 5 and 9) belonged to the skin negative or infective group. In these two patients it was difficult to evaluate the benefit obtained because they had mild wheezing and cough only during extremes of temperature. Moreover, when a placebo was given them similar relief was reported. The other five patients belonged to the mixed group (allergic and infective—Cases 3, 4, 17, 21 and 30). They received the usual allergic management in conjunction with benadryl.

TABLE II

COMPLICATING PATHOLOGICAL CONDITIONS PRESENT IN TWENTY-THREE ASTHMATIC PATIENTS UNRELIEVED BY BENADRYL

Pathological Conditions	No. of Patients
Sinusitis	8
Sinusitis Bronchitis	2
Sinusitis Bronchiectasis	1
Sinusitis Emphysema	2
Chronic bronchitis Emphysema	2
Chronic bronchitis Emphysema Bronchiectasis	1
Chronic bronchitis Emphysema Arteriosclerotic heart disease	1
Chronic bronchitis Syphilis	1
Pulmonary tuberculosis	1
Emphysema Coronary sclerosis	1
Arteriosclerotic heart disease Auricular fibrillation Emphysema	1
Arteriosclerotic heart disease Cardiac decompensation Coronary sclerosis	1
Coronary sclerosis Bundle branch block	1

CASE 3. A female, age forty-eight, had slight wheezing daily for the past eight years. She took thyroid extract for hypothyroidism and obesity. She was highly emotional. Her symptoms lessened for eight weeks on an intake of 150 mg. of benadryl per day. When she was given a placebo for two weeks her symptoms became worse. When she took 300 mg. of benadryl a day she had complete relief.

CASE 4. A male, age seventy-five, had mild asthma for the past thirty-two years. *X*-ray examination of his lungs showed healed pulmonary tuberculous lesions. His asthmatic symptoms occurred during extremes of temperature and during the hay fever season. When given 150 mg. of benadryl per day there was no improvement. When benadryl was increased to 300 mg. per day he became symptom-free. When a placebo was substituted for the benadryl the asthmatic attacks recurred.

CASE 17. A female, age twenty, had daily asthma for the past nine years. Prior to treatment with benadryl she suffered from severe asthma as the result of an acute sinus infection. She required intravenous aminophyllin for relief. When the sinus condition improved she was given 150 mg. of benadryl daily and reported that there was a marked improvement in her asthmatic condition. When a placebo was substituted for the benadryl her condition remained the same. She had no further sinusitis while under observation.

CASE 21. A female, age 26, had asthma for the past eight years. Intracutaneous tests showed her to be markedly sensitive to house dust and animal danders. She was subject to occasional attacks of sinusitis and was highly emotional. Her asthmatic attacks became milder on an intake of 300 mg. of benadryl daily. The substitution of a placebo was followed by a recurrence of her asthma. She has had no sinusitis while under observation.

CASE 30. A female, age forty-seven, had asthma for twenty-five years. During the summer months her asthma occurred in association with early and late hay fever symptoms. During the winter months she had frequent acute sinus infections which were accompanied by chest symptoms. When given 150 mg. of benadryl a day her nasal and chest symptoms were greatly decreased in severity. The nose and chest symptoms at this time were the result of pollinosis. When she took 100 mg. of benadryl at bedtime her symptoms diminished sufficiently to insure a good night's sleep.

Twenty-three of the thirty patients or 77 per cent treated with benadryl failed to obtain any relief whatsoever. All of them showed organic changes in the lungs or heart or an active sinus infection. (Table II.) In some cases the drug seemed to aggravate the asthmatic symptoms but it was deliberately increased with no relief. When benadryl was used in conjunction with other anti-asthmatic drugs such as ephedrine, potassium iodide or aminophyllin the relief obtained was greater than when the latter drugs were used alone. Benadryl was found to be especially helpful when administered in 100 mg. doses at bedtime. Such a procedure usually insured restful sleep.

A slight fall in blood pressure was noted in twenty-two of the thirty patients following the administration of 50 and 100 mg. doses of benadryl. No significant changes in vital capacity followed the use of this drug.

SIDE REACTIONS

The majority of the patients, twenty-eight or 93 per cent, complained of ill effects while using benadryl. Drowsiness occurred in all twenty-eight, dizziness in twenty-three, dry mouth in three and fatigue in two of the patients. Six patients refused to continue the drug because of these untoward reactions (Cases 6, 13, 14, 23, 25 and 28). These symptoms disappeared when the drug was discontinued and reappeared when again used. In three of these patients (Cases 13, 14 and 23) the side reactions were so severe as to warrant discontinuance of the drug at an earlier date but they were prevailed upon to continue it in order to note any tendency to overcome such reactions.

COMMENTS

Benadryl has been shown to possess high anti-histaminic properties in animal experimentation. Clinically the drug demonstrates a pronounced action on the allergic wheal. It diminishes the reaction of the skin to histamine and has proven of value in the treatment of such conditions as urticaria,

angioneurotic edema and serum sickness and in relieving the itching of various types of dermatitis. The reports on the therapeutic value of benadryl in bronchial asthma have not been definitely established.

To evaluate the effect of this drug on the symptoms of bronchial asthma it was administered to thirty adults who had experienced asthmatic attacks for many years with little relief from the usual asthmatic remedies. The majority of the patients were middle aged or elderly individuals with advanced stages of bronchial asthma and with organic disease of the lungs, heart or paranasal sinuses. There were no infants or children in this group.

Benadryl, administered in dosages of 150 to 400 mg. daily, produced symptomatic relief in 23 per cent of the patients. This improvement was only temporary and palliative. When the drug was of help, 50 to 100 mg. controlled the cough and wheezing for from four to eight hours. These patients had no complicating conditions in the lungs or heart, and their asthmatic symptoms could not be attributed to acute respiratory infections. When the asthmatic symptoms occurred as a result of nasal allergy especially pollinosis, benadryl relieved the nasal symptoms and lessened the severity of the chest symptoms.

Seventy-seven per cent of the patients obtained no relief whatsoever while using benadryl alone. All of them showed either organic lung or heart disorders or acute infections in the paranasal sinuses. However, when the drug was prescribed in conjunction with other anti-asthmatic remedies such as ephedrine, potassium iodide or aminophyllin it proved of further help in relieving the symptoms.

Benadryl seems to be of limited therapeutic value in controlling the symptoms of bronchial asthma. The drug was ineffective when the asthma was precipitated or complicated by respiratory infections, especially acute sinusitis, or when organic changes of the lungs or heart were present. Severe asthmatic episodes were uninfluenced by benadryl administered orally regardless of the etiology. The blood pressure was slightly lowered in twenty-two of the thirty patients and the spirometer readings remained unchanged following use of the drug. The side reactions of the drug in producing drowsiness, dizziness and other ill effects obviated its continued use for long periods of time. The edema and spasm of the bronchial musculature producing the asthmatic symptoms cannot be explained solely on the basis of the liberation of histamine. Other physiologic changes are probably involved. However, there is enough hope in drugs of this nature to warrant further experimentation for a substance with greater therapeutic value and better tolerance. Such a compound has been synthesized and clinical studies are now in progress.

SUMMARY

1. Benadryl was administered orally in dosages of 150 to 400 mg. daily to a group of thirty adult asthmatics who were resistant to all forms of the usual asthmatic remedies.

2. Seven or 23 per cent of the patients experienced symptomatic relief. Withdrawal of the drug was followed by recurrence of symptoms.

3. Benadryl was beneficial to those patients whose asthmatic symptoms were not due to acute upper respiratory infections or to demonstrable organic lesions in the lungs or heart.

4. Twenty-three or 77 per cent of the patients failed to obtain any relief whatsoever. All of them showed organic changes in the lungs or heart or an active sinus infection.

5. The drug was without immediate effect upon severe attacks of asthma, regardless of etiology.

6. Benadryl was found to be helpful when

used in conjunction with known anti-asthmatic drugs.

7. Side reactions such as drowsiness, dizziness, dry mouth and fatigue occurred in twenty-eight or 93 per cent of the patients.

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Diagnosis of Brill's Disease (American Form of European Typhus Fever) by Skin Biopsy*

HARRY MANDELBAUM, M.D. *and* GEORGE HOLLANDER, M.D.

BROOKLYN, NEW YORK PHILADELPHIA, PENNSYLVANIA

EPIDEMICS of classical typhus fever have broken out periodically in Central Europe for many hundreds of years and in the United States as late as the nineteenth century. The etiological agent was established by the brilliant work of Howard Taylor Ricketts in 1910 and the organism now bears his name. At present several varieties of the rickettsial diseases are found in the United States. Because of recent advances in treatment, both with immune serum and with para-aminobenzoic acid, early diagnosis is of extreme importance since present treatment, to be effective, must be started within the first week of the disease. We present here a simple practical procedure for the early diagnosis of the rickettsial diseases.

In 1910, Brill[1] published a series of cases which strongly resembled epidemic (classical or European) typhus fever. Most of Brill's patients with the disease had immigrated here from the typhus regions of Europe. It was therefore not clear whether the disease represented classical typhus (either as an importation from Europe or as a recurrence of latent infection) or was of local origin, possibly flea-borne. Several years later a somewhat similar typhus-like disease was described in Georgia[2] and since then thousands of cases have been reported, particularly from the Southeastern section of the United States. The term "Brill's disease" was at first applied to these cases; however, it soon became evident that the typhus fever seen in the Southeastern part of the country differed from the disease described by Brill.

The confusion surrounding the rickettsial diseases led many[3-5] to believe that both Brill's disease and Southeastern (murine) typhus were solely of native origin. In 1934, Zinsser[6] represented Brill's disease as a recrudescence of an old attack of typhus fever. Plotz[7] subsequently demonstrated the immunological identity of Brill's disease with classical typhus, separating it from the endemic (murine) form of typhus. Using the complement fixation technic in twenty-three cases of Brill's disease, Plotz found that the pattern of fixation in this disease resembled that obtained in epidemic typhus fever. His studies indicated that mild cases of epidemic typhus actually exist in the United States in a sporadic form. Apparently one attack of typhus does not confer a lifelong immunity as was generally believed. The virus may be harbored in the body and with lowering of the resistance of the host the virus may multiply and induce a mild attack of the disease. Man may serve as a reservoir for epidemic typhus between outbreaks of the disease just as the rat does in endemic typhus.

It is probable that many of the cases previously reported in the Northeastern United States as Brill's disease and which occurred in native Americans would now be classified as Rocky Mountain spotted fever; laboratory data necessary for accurate differentiation of the typhus-like fevers were lacking at the time these reports were made.

* From the Department of Medicine, The Jewish Hospital of Brooklyn, Brooklyn, N. Y.

In fact, of three cases reported by Flippin,[8] the author admits that two probably represented cases of Rocky Mountain spotted fever; one had given a definite history of tick bite.

These earlier attempts to classify the rickettsial diseases occurring in the United States resulted in much confusion. The same disease has been described under different names and the same terminology has been applied to separate disease entities. At present there seem to be three distinct types of rickettsial disease in this country. It now seems advisable to classify them as first, the *American form of European typhus fever*, which represents Brill's disease and occurs in the northeastern part of the country; second, *murine typhus*, which has the rat flea as a vector and is endemic to the southeastern part of the country, and third, *Rocky Mountain spotted fever*, with ticks as the vectors and occurring throughout the United States.

The etiological organism is a small polymorphous micro-organism, the Dermacentroxenus rickettsia; R. prowazeki is responsible for the classical form of typhus fever; R. mooseri, for the murine type and R. rickettsii for Rocky Mountain spotted fever. Both Plotz[9] and Felix[10] have demonstrated that the morphological variations in the different types of rickettsiae are not to be regarded as indicating specific morphological differences. Since they are so strikingly similar in appearance (excepting the organism responsible for tick-borne Q fever), the following description is applicable to all types seen in the United States.

The organism stains best with Giemsa stain and other special stains. When stained with Giemsa stain in the usual fashion[11] they appear to be larger and more distinct. Early, Pinkerton[3] described the rod forms of the organism and thought that the cocci seen were paired rods seen standing on end. They appeared as minute diplobacilli, 1.2 by 0.3 microns to 1.6 by 0.3 microns. The organism is non-filterable and appears as short and long chains, occasionally as a filamentous form. Using Giemsa stain, Sikora[12] clarified the description of the various forms of the organism showing how each type corresponded to a different stage in growth and development. These included (1) round or oval non-cellular granular forms, each of which elongates to form (2) a short, rod-shaped or barrel-shaped cellular body with a granule at each end which further elongates and subdivides into (3) a bacilliform body containing three or four granules in each. Each bacilliform body then divides into (4) two plump bodies, each of which has two polar granules which elongate and become (5) dumbbell shaped. More recent studies of the Rickettsiae with the aid of the electron microscope[9,13] show them to be pleomorphic, with both rod-like and coccal forms. The bacillary forms are seen to have a limiting membrane enclosing a substance which is moderately opaque to electrons; in some cases spherical granules are seen within the organism. Some forms are completely opaque while others are transparent. The smaller coccoidal forms, which cannot be distinguished with certainty from tissue particles by ordinary methods, have the same structural appearance as the bacillary forms. These studies apparently confirm the belief that the Rickettsiae occupy a position intermediate between bacteria and the filterable viruses.

The essential pathologic changes in all rickettsioses are similar with minor variations which will be described. Frankel[14] in 1914 described the histological appearance of the lesions in classical typhus fever. The changes are an expression of intrinsic vascular, usually intimal, damage due to the multiplication of the Rickettsiae in the lining of the endothelial cells or in the smooth muscle cells of the blood vessels.

The extent of the damage depends upon the character and virulence of the particular rickettsial infection. The presence of these organisms[15] causes swelling and proliferation of the endothelium, cellular infiltration of the vessel walls, perivascular accumulation of mononuclear cells and occasionally thrombosis and hemorrhage. The vessels appear to be enclosed by a sheath of infiltration. These vascular changes are of the same general type throughout the body and usually affect the smaller vessels of the skin, brain, lungs and heart. The proliferative endangiitis involves the arterioles, capillaries and at times the venules; occasionally the larger vessels are also involved. In classical typhus this swelling and proliferation of the infected endothelial cells in the small vessels causes occlusion more frequently than in mite typhus fever.

The skin is one of the chief organs in which these characteristic vascular changes occur and the skin macules show inflammatory involvement of the small blood vessels with endothelial proliferation. The perivascular infiltration[16] consists chiefly of lymphocytes with a few polymorphonuclear cells. Escape of blood from the damaged vessels is the basis of the petechiae. The accumulations of mononuclear cells form small nodular lesions; these are characteristic and are seen more commonly in the skin and brain. In classical typhus fever[17] the capillary thrombi, while not constantly present, are more conspicuous when they do occur and the endothelial cells are more obviously damaged. There is also a tendency to a necrotizing arteritis which is not found in the mite form of typhus fever. The macules in Rocky Mountain spotted fever[17,18] resemble those of classical typhus. Here, also, Lillie[19] has shown numerous perivascular foci of lymphocytic infiltration with swelling of the capillary endothelium and concentric proliferation in the skin. Thromboses of the arterioles and venules were uncommon.

Rickettsiae have frequently been demonstrated in the cytoplasm of the endothelial cells of the vascular lesions. Pinkerton[3,20] described their appearance in the vessels of the brain and skin. Lillie[19] noticed that they were easily found in many of his cases.

CLINICAL PICTURE OF BRILL'S DISEASE

The onset is abrupt and a shaking chill is not uncommon. Headache, backache and pyrexia are prominent. The headache is excruciating and usually is not relieved by the common remedies; resort to spinal tap may bring appreciable alleviation. Backache and generalized muscular aching are troublesome. Malaise and gastrointestinal symptoms are common. The fever rises rapidly, is continuous and unremitting and falls by crisis or lysis about the tenth or twelfth day. The conjunctivae are injected, occasionally accompanied by photophobia and lacrimation. Some nuchal rigidity is evidenced. Drenching sweats, tinnitus and deafness are common. Early prostration is characteristic of the disease in contrast to the first week of typhoid fever. It resembles more closely the exhaustion of the third week of typhoid fever.

The rash usually appears on the fourth day; its appearance is rarely delayed as late as the seventh day. A constant succession of lesions occurs; first over the anterior axillary folds and sides of the abdomen and then it spreads peripherally to involve gradually the chest, back, shoulders and extremities in that order. It may involve the dorsum of the foot and the back of the hands. As a rule, it spares the palms of the hands, the face and the neck. It rarely itches. The lesions appear as irregular, round or oval elevated areas of macular eruption, 1 to 5 mm. in diameter, pink to bright red, disappearing on pressure except when they become hemorrhagic. Rarely, the lesions

may become necrotic. Characteristic of the rash is its irregular distribution, the depth of color and its outline.

The nervous symptoms parallel the degree of central nervous system involvement. A non-productive cough occurs in about half the patients. Pneumonia is not uncommon and may protract the course.

The mortality rate of Brill's disease rarely exceeds 1 to 2 per cent. Fatalities are usually confined to the encephalitic forms and to older patients with accompanying myocardial or renal complications. This compares with a mortality rate of 6.1 per cent in 2,233 patients with murine typhus[21] reported during 1938.

Diagnosis. Weil and Felix[22] first described an agglutination test giving a response with Proteus organisms, OX 19 strain. It is significant if elevated above a 1 to 80 dilution. Stuart and Pullen[23] reported that in 180 cases of murine typhus fever no test was positive before the fifth day. In this series ninety-five tests failed to reveal the presence of agglutinin; the average time after onset when these tests were made was 6.8 days. The average time required for the appearance of agglutination titers of 1 to 80 was 8.5 days; 1 to 160, 10.5 days; 1 to 320, 11.4 days; 1 to 640, 13.3 days and 1 to 1,280, 15.9 days.

The proteus reactions do not differentiate between louse-borne typhus, Brill's disease and murine typhus.[10] In Rocky Mountain spotted fever the reaction is highly irregular. The complement fixation technic described by Plotz[24] has proved adequate for serological separation of the rickettsial agent of endemic typhus, Q fever and Rocky Mountain spotted fever but it was of no help in differentiating between epidemic and endemic typhus fever. With the use of prepared rickettsial antigens[7] epidemic and endemic typhus fever can be differentiated. Van Roogen and Bearcraft[25] reported on the use of specific agglutination tests against Rickettsia. In seventy-two cases of typhus fever there was correlation between the Weil-Felix reaction and the rickettsial agglutination test. Both tests, however, are seldom positive before the seventh day of the illness, two to three days after the appearance of the rash. The rickettsial agglutination test reactions are maximum about the fourteenth day of the illness and may persist for as long as two years, as compared with the proteus agglutination which fades rapidly.

So pathognomonic of typhus fever is the pathological picture of the lesions in the arterioles and capillaries that biopsy of these was suggested as a diagnostic procedure as far back as 1914,[14] and more recently by Pinkerton.[20] However, to our knowledge this procedure has never been adapted as a diagnostic aid.

The clinical pattern presented in patients with suspected rickettsial disease challenges proper interpretation even after appearance of the rash. The serological tests are seldom of help until the third or fifth day, or longer, after the appearance of the eruption. It is well known that a large percentage of cases will give a negative response to the Weil-Felix reaction. Many hospital laboratories are not equipped to perform the newer rickettsial complement fixation and agglutination tests; therefore, we suggest this practical and simple method for the early diagnosis of rickettsial fevers.

A well developed lesion, preferably of a macular type, is excised with ample underlying tissue. It is fixed in Regaud's fluid and stained using the usual Giemsa method. An experienced pathologist can easily recognize the characteristic lesions even in the absence of the rickettsial bodies. In classical typhus, Brill's disease and murine typhus the Rickettsiae may be found in the endothelial cells lining the blood vessels. Even in the absence of the organism the proliferative endangiitis is diagnostic. In Rocky Mountain spotted

fever the Rickettsiae rarely will be seen in the smoother muscle cells of the arterial walls.[20]

CASE REPORTS

CASE 1. A thirty-nine year old white female was admitted to the Jewish Hospital of Brooklyn complaining of fever, headache, vomiting and generalized body aching for a duration of four days. She was born in Poland and had been a resident of the United States for the past twenty-six years. At the age of five she had contracted typhus fever during the European epidemic of the first World War. The remainder of her past history and family history was irrelevant.

Four days before admission to the hospital she became ill with a fever of 105°F. This was accompanied by severe frontal headache, generalized aching and nausea. A shaking chill was present every morning. The fever continued remittent, reaching a peak at 3 P.M. and again at 1 A.M., never returning to normal. It was accompanied by marked sweating. For the two days preceding admission there had been constant vomiting; diarrhea, with loose, watery stools was present the day before admission.

Physical examination showed a well developed, well nourished white female who appeared acutely ill. The temperature was 103°F. with a pulse rate of 100 per minute. The face was flushed and the patient exhibited marked photophobia and hyperesthesia. The eyes had a feverish, glassy appearance. There were several pinkish macular areas over the abdomen which faded on pressure. The remainder of the physical examination was normal with the exception of an enlargement of the spleen which was felt two fingers below the costal margin.

A spinal tap performed on admission showed 68 cells per cu. mm. These were predominantly lymphocytes. There was a slight trace of protein. Sugar and culture of the spinal fluid were negative. Another spinal tap repeated on the third hospital day showed a clear fluid without cells. Routine studies on this fluid were negative.

The macular rash became more prominent on the second hospital day but still continued to fade upon pressure. It had now spread over the chest and back as well as the abdomen, and some of the macules did not blanch with pressure. The rash began to fade on the fourth day until it was barely visible on the eleventh hospital day.

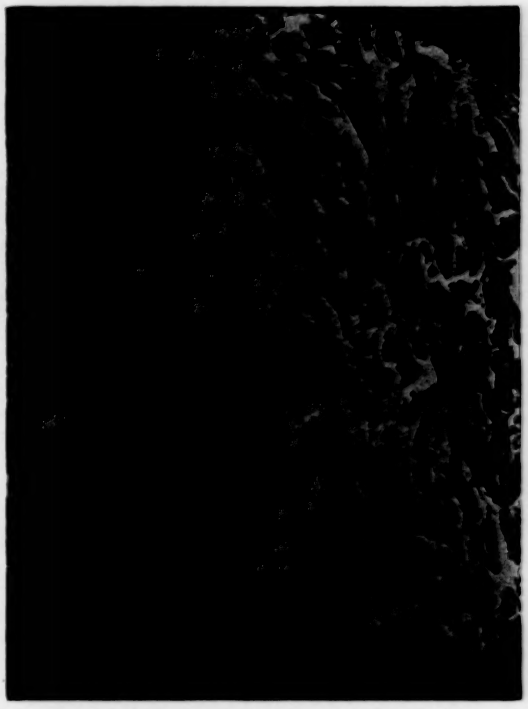

FIG. 1. Section of skin macule. Blood vessels within corium are distended. There is proliferation of the endothelium. The blood vessels are surrounded by a collar of inflammatory cells which consist of polymorphonuclear leukocytes and small and large mononuclear cells; hematoxylin and eosin stain × 600.

During the first week of hospitalization the patient had an intermittent fever ranging from 100.2°F. to 103.4°F. Penicillin, 50,000 units every three hours, was given intramuscularly for the first week without apparent effect. The temperature fell by lysis and reached normal on the ninth hospital day (the thirteenth day of the illness). At this time the spleen was barely palpable. Convalescence was uneventful and the patient was discharged on the seventeenth hospital day.

The laboratory studies showed several urine examinations to be normal. A slight secondary anemia was present with a leukocyte count of 3,550 and a normal differential count. The leukocyte count rose progressively during the illness until it reached 8,450. The sedimentation

FIG. 2. A, section of skin macule. The blood vessels of the upper part of the corium show swelling of the endothelial cells and granular degeneration of the cytoplasm. The swollen cells are filled with minute, bluish-black coccoid bodies in clumps within the cytoplasm; Giemsa stain × 2255.

rate was 25 mm. (Westergren) in one hour. The Kline test was negative. Many blood and stool cultures were negative. Repeated agglutination studies for typhoid, paratyphoid, tularemia and brucella were negative. The heterophile agglutination titer was 1 to 8 and later 1 to 32. Proteus OX 2 and 19 agglutination reactions taken on the sixth hospital day were negative.

A skin biopsy of a macular lesion from the abdomen was taken on the third hospital day. Microscopic examination (Fig. 1) showed distended blood vessels within the corium, the endothelium of which was somewhat swollen. Surrounding some of these were collars of inflammatory cells. The cells included polymorphonuclear leukocytes as well as small and large mononuclear cells. With Giemsa stain some areas showing dark coccoid bodies were seen but they could not be definitely identified as rickettsiae. The pathological picture showed a toxic vascular disease that was compatible with that seen in typhus fever.

CASE II. A thirty-four year old white truck driver was admitted to the Jewish Hospital after eight days of fever. He was Russian-born and had been in the United States for the past twenty-four years. As a child in Russia he had had a severe febrile disease accompanied with pneumonia. There was no other recollection of illness previous to this admission.

His illness began on the eighth day before admission with severe frontal headache which was aggravated on bending forward and which lasted for two days. That night he noted a fever of 102°F. The persistance of the fever led him to call a physician two days later. In spite of oral penicillin and antipyretics every three hours the fever continued intermittently, with daily rises as high as 105°F. in the morning and evening and down to 101°F. during the afternoon. During this period the frontal headache reappeared and was severe enough to prevent him from sleeping. There was no pain on movement of the eyeball. Another physician who saw the patient the day before admission placed him on sulfadiazine every four hours; this therapy had been continued until admission. The temperature curve had remained unaffected. He had not noticed the presence of a rash until it was brought to his attention upon admission.

When admitted the patient appeared apathetic with a flushed face. His temperature was 101.8°F. (rectal) with a pulse rate of 92 per minute. There was a diffuse, red, maculo-papular erythematous rash over the arms, axillae and back. The macules were discrete, about 1 cm. in diameter and disappeared on pressure. No nuchal rigidity was present. Some few nontender anterior cervical glands were felt. One large axillary node was palpable on the right side. With the exception of a palpable spleen, felt two fingers below the costal margin, the remainder of the physical examination was negative.

The hospital course was uneventful. With only symptomatic treatment, the fever which had ranged from 100°F. to 104.4°F., fell by lysis and the temperature reached normal on the thirteenth hospital day. The pulse remained slow in relation to the fever. Soon after admission the rash began to subside and disappeared completely on the eighth hospital day, having

FIG. 2. B, section of skin macule; Giemsa stain × 2255.

lasted until the sixteenth day of the illness. The spleen was not palpable after the sixth hospital day.

The laboratory findings showed several urine examinations to be negative. The hemoglobin and erythrocyte count were normal. On admission the leukocyte count was 11,050 with a normal differential count. It gradually fell to 8,700; the differential count showing an increase of lymphocytes from 22 to 45 per cent. The sedimentation rate was 78 mm. (Westergren). The Kline test was negative. Blood sugar and urea were within normal limits. Agglutinations for typhoid, paratyphoid, salmonella and brucella groups were negative, as were several blood cultures taken throughout the course of the illness. The heterophile antibody titer on admission and again on discharge was 1 to 16. Several stool cultures were negative. The Weil-Felix reactions for Proteus OX 2 and 19 were negative upon admission as well as ten days after discharge. Two months after the patient was discharged the Weil-Felix reaction showed a titer of 1 to 40 for Proteus OX 19. An electrocardiogram was within normal limits.

A skin biopsy was taken of a macule on the left chest on the sixth hospital day. Microscopic examination (Fig. 2A.) showed normal epidermis. The blood vessels of the upper part of the corium showed some swelling of the endothelial cells with some granular degeneration of the cytoplasm. There were occasional large histocytic cells near these blood vessels. A special stain (Giemsa) (Fig. 2B.) showed many of these swollen cells to be filled with minute bluish-black coccoid bodies in clumps within the cytoplasm. In some instances they occupied the entire cell. These were probably the inclusion bodies described as Rickettsiae.

SUMMARY

1. In the United States at present there seem to be three distinct types of rickettsial disease. Brill's disease (the American form of typhus fever) is found in the northeastern part of the country, murine (flea-borne) typhus occurs mainly in the southeastern part of the United States while Rocky Mountain spotted fever (mite-borne) occurs throughout all parts of the country.

2. The pathological changes caused by Rickettsiae are essentially similar. These characteristic vascular changes consist of vasculitis and perivasculitis. If carefully looked for, the Rickettsiae may be found in the endothelial cells lining the blood vessels. The vessels usually affected are the smaller ones of the brain, lungs, skin and heart.

3. Successful treatment of the typhus group of fevers for the present depends upon starting therapy within the first week following the onset of the disease. Because of the difficulties in carrying out specific complement fixation and agglutination tests for Rickettsiae, a simple method of early diagnosis by skin biopsy is described.

4. Two patients with Brill's disease with characteristic clinical and pathological changes in the skin are presented. In one of the subjects, the rickettsial organisms were identified.

We are indebted to Dr. Irving Holtzman for aid in interpretation of the pathological slides.

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Virus Pneumonia

GUY R. MCCUTCHAN, M.D.

PORTLAND, OREGON

PRIMARY atypical pneumonia, etiology still unknown, has become sufficiently prevalent since 1937 that a large number of publications have been devoted to its description.

Little more than a decade ago such cases were either exceedingly rare or went unrecognized. At that time the writer, during the course of two severe winters on a large pneumonia service, cannot recall more than three or four instances in which a clinical picture compatible with the modern concept of atypical pneumonia was encountered.

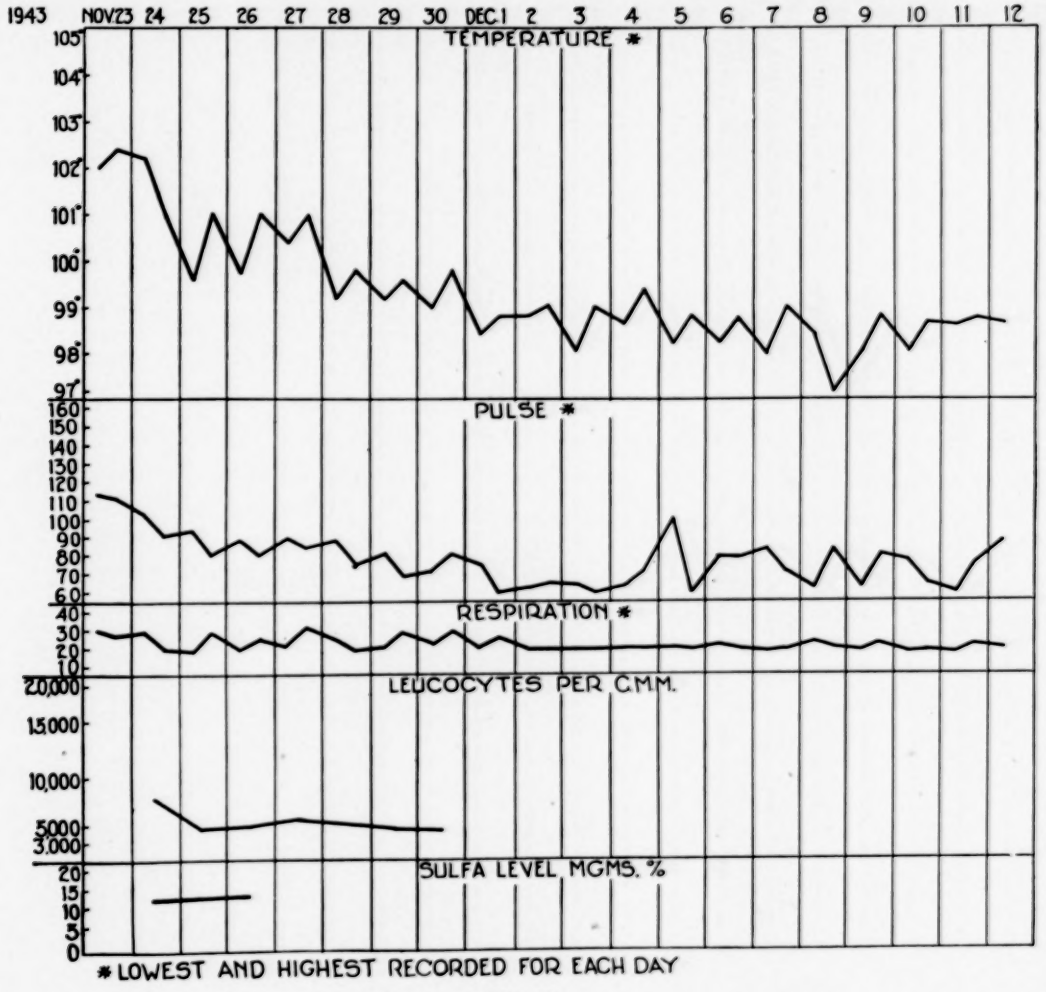

FIG. 1.

Does this mean that the incidence of this kind of pneumonia is increasing? It undoubtedly does because so many reports[1–6] have described a steadily increasing number of cases. In some army camps over 50 per cent, perhaps up to 75 or 80 per cent, of all pulmonary lesions have been primary

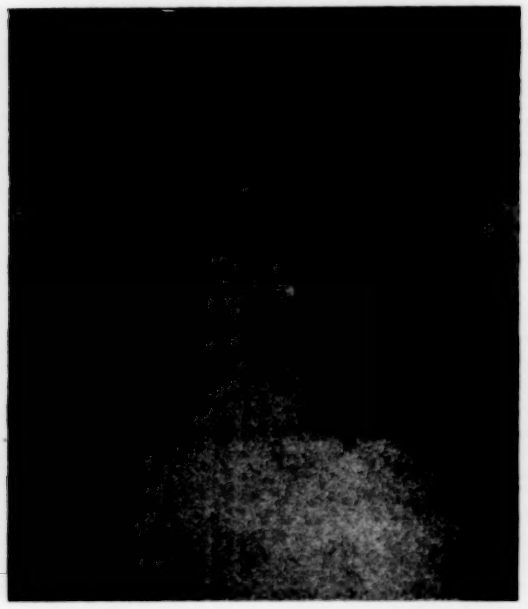

FIG. 2. Note the lacy infiltration, right base.

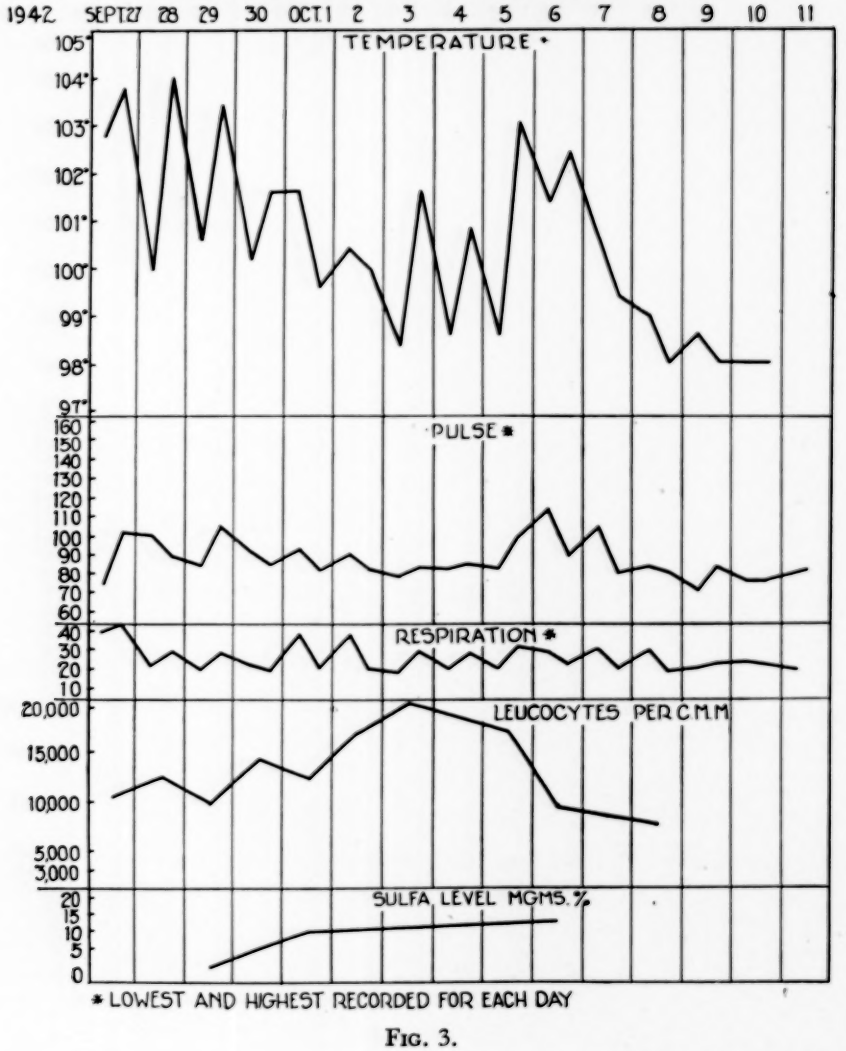

FIG. 3.

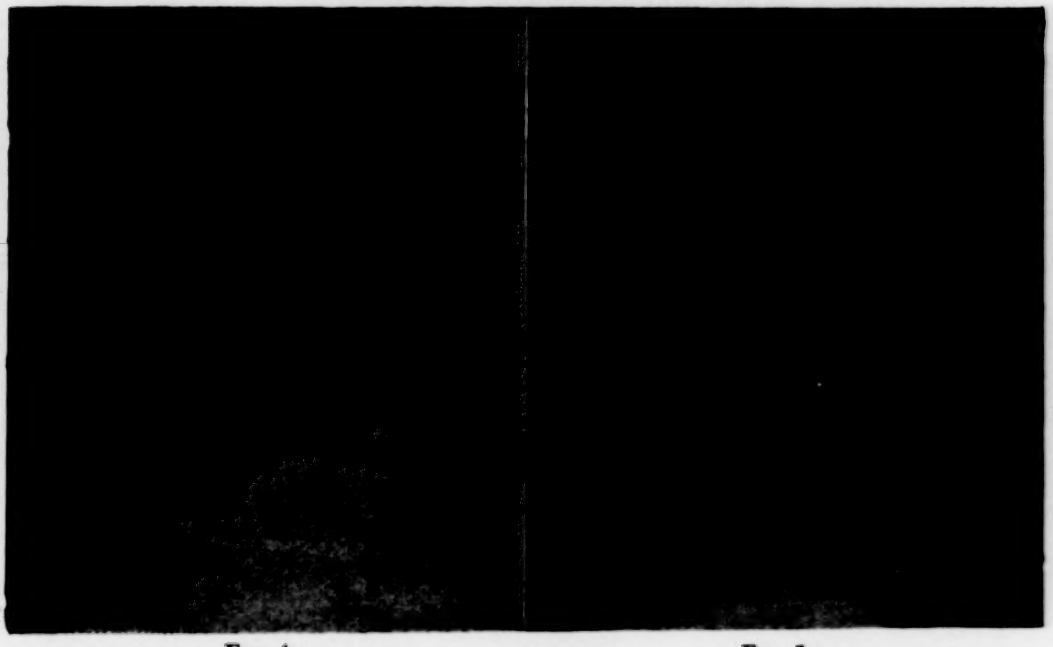

FIG. 4. FIG. 5.

FIGS. 4 and 5. Involvement is extensive throughout the upper lobe (Fig. 4) but not very dense. Patchy pneumonitis (Fig. 5) in almost the entire right lung.

atypical pneumonia.[7] Statistics in the civilian populace have not been so readily available but as high as 50 per cent of some communities have been involved because of a common viral agent.[8]

All are agreed that primary atypical pneumonia is not a new disease. Interstitial pneumonitis, a pathological picture indistinguishable from that produced by so-called "virus pneumonia," was fully recounted in the days of the Civil War.[9] Likewise, both the clinical course and lung findings in the influenza pandemic of 1918 were very similar to those reported in present day autopsies of patients who died of primary atypical pneumonia.[10]

Ample opportunity for detailed study of a fair number of cases has been afforded every internist. Continued interest in the subject may result not only in fuller understanding of the disease as a whole but may well lead to definite recognition of the causative agent.

The present paper is based on an analysis of sixty-one cases which were studied between 1942 and 1944. These patients had all of the criteria essential to the diagnosis of primary atypical pneumonia: a respiratory disease of insidious onset, non-bacterial in nature, sometimes more striking roentgenologic findings than anticipated (more to be said on this later), leukopenia, normal white blood count or moderate leukocytosis, pulse and respirations low in relation to the temperature and failure of response to sulfonamides.

The etiological aspects of virus pneumonia have been fully discussed by Reimann et al.[12] and many others.[13,14] While current opinion favors the notion that the majority of cases of atypical pneumonia are due to some type of virus, it appears that other agents may be responsible for atypical pulmonary infection. The pathology has been adequately described elsewhere.[14,15]

The clinical course in this disease is most variable and statements made concerning the severity of "virus" pneumonia are often grossly erroneous. That it is a mild or benign affliction may be true in most

instances, but it should also be pointed out that examples of critical illness are not unheard of, as one of my case reports will show. Some authorities have flatly stated that atypical pneumonia is not a contagious disease[11] but this is most fallacious. Others have stressed the low transmissibility to contact, but most authorities agree that it is highly communicable. The author had three cases in a family of five (the remaining two had a cold and cough) and another family of three in which all had "virus pneumonia" at the same time. Two of the last cases will be reported, but the father is not included because he was neither hospitalized nor *x*-rayed.

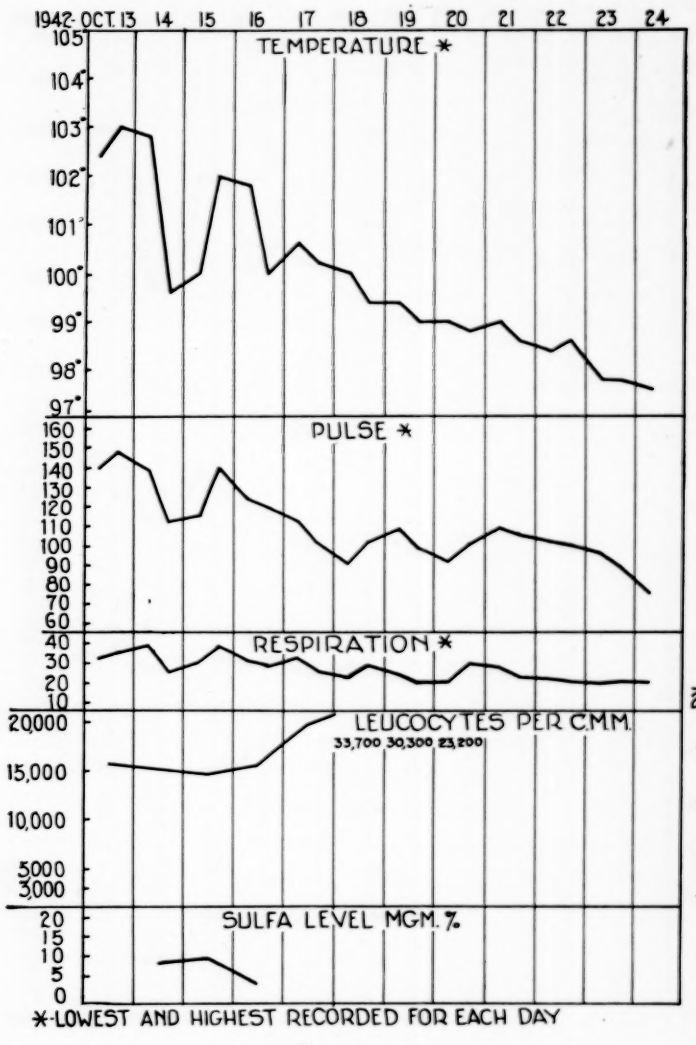

FIG. 6.

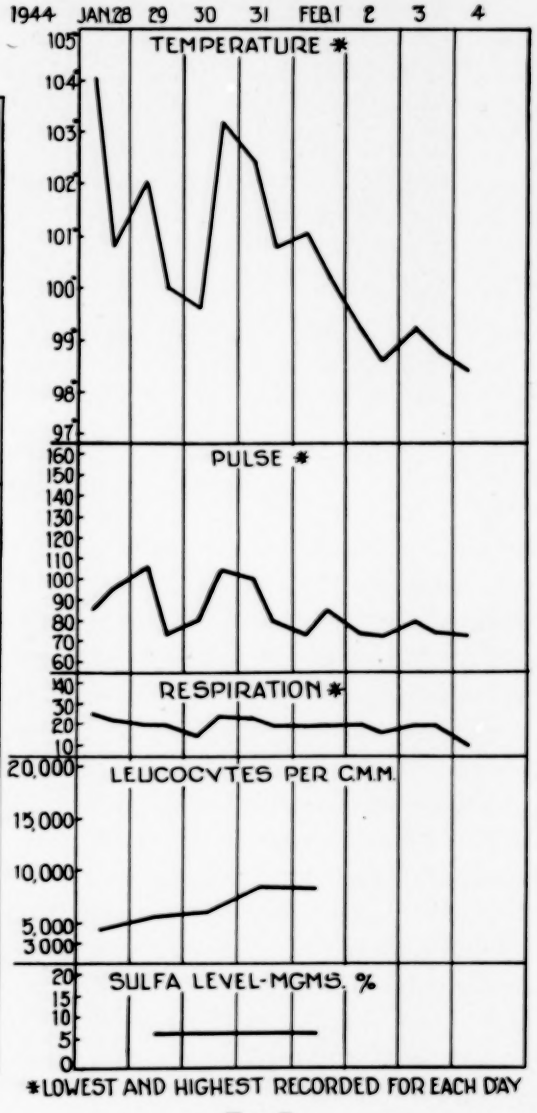

FIG. 7.

CASE REPORTS

The following brief case reports, roentgenograms and graphs are presented to demonstrate some of the clinical aspects of this syndrome:

CASE 1. Mrs. W. A. S., a thirty-nine year old nurse, had been ill for about a week previous to her admission to the hospital on November 23, 1943. She had been having a slight fever, a dry non-productive cough, malaise, headache, feeling of extreme fatigue and depression. The day

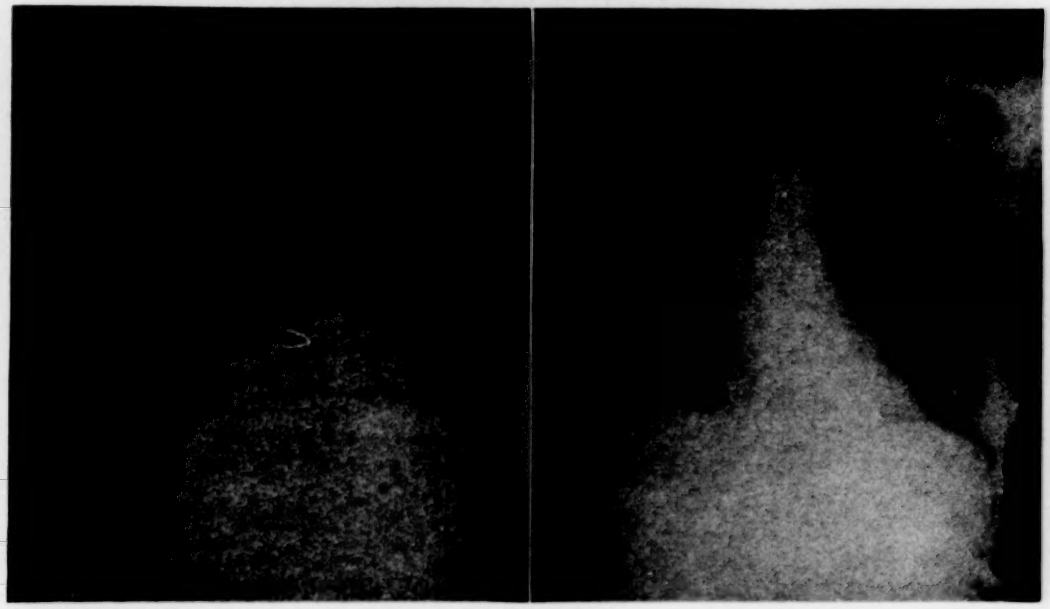

FIG. 8. The involvement here is chiefly right lower but there is also a patchy infiltration in the left lower lung field.

FIG. 9. This is one of the very occasional cases in which the *x*-ray findings were far more extensive than suspected.

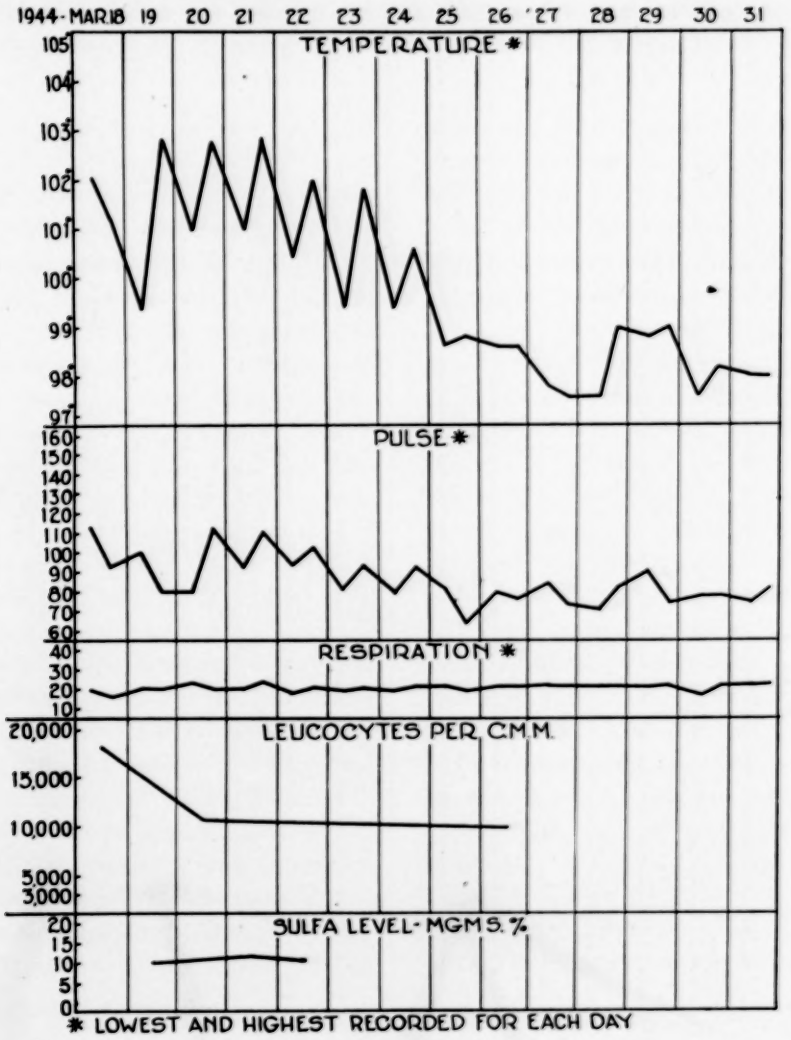

FIG. 10.

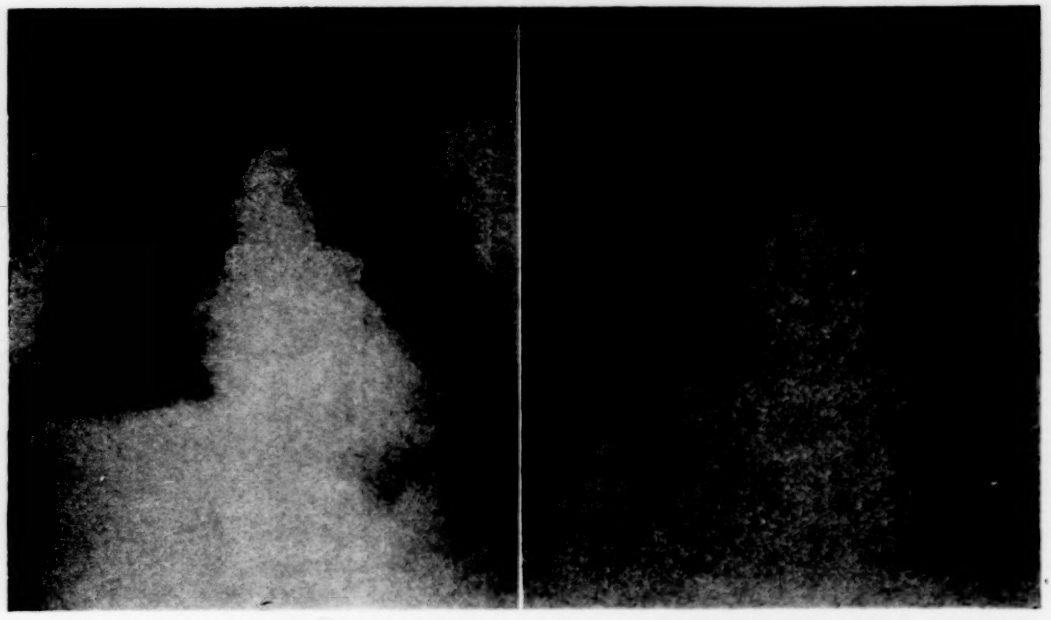

FIG. 11. FIG. 12.

FIGS. 11 and 12. The lesion in the right upper in this instance (Fig. 11) had to be differentiated from tuberculosis. Recheck chest plate (Fig. 12) of patient shown in Figure 11 only six days later exhibits complete clearing of the right apex and the appearance of a small patch in the left lower lobe.

she was first examined, November 23, 1943, she did not appear acutely ill and her temperature was only 101.2°F. Physical findings were limited to slight impairment of resonance at the right base, and a few crackling râles upon deep inspiration; there was no suggestion of bronchial or tubular breathing.

From Figure 1 it is obvious that the fever was highest when the sulfadiazine level was 12 to 13, that the pulse is slow in relation to the temperature, and that the white blood count ranged from 4,000 to 7,900. It is worth noting that the roentgenologist in reporting the *x*-ray of this patient's chest (Fig. 2) stated without reservation, "virus pneumonia, right base." No organisms could be typed or grown from the sputum. Weakness and easy fatigability persisted in this patient for six weeks after recovery.

CASES II and III. Mrs. G. M. H. was twenty-seven years of age and her daughter, H. H., was aged three. The mother in this family of three became ill September 24, 1943, with chills, fever, headache, chest pain and later a hacking cough productive of a whitish, frothy sputum. She entered the hospital September 27, 1943, and at that time had dullness and râles in the left upper chest. She was quite acutely ill and Figure 3 shows that the course of her temperature, etc., were not influenced by an adequate sulfa level and that coincident with the second elevation in temperature there was considerable leukocytosis. In the chest film (Fig. 4) pneumonitis of the left upper lobe is apparent. While this patient was in the hospital, her three-year-old daughter and husband became ill with cough, chills and fever. The former entered the hospital with a patchy pneumonitis involving most of the right lung. (Fig. 5.) The author is not so familiar with this type of pneumonia in children, but Figure 6 indicates that considerable leukocytosis may be present. The lack of response to sulfa is again exhibited. The husband and father of these patients had virus pneumonia at the same time but was treated at home. These cases illustrate that at least in some instances the disease is highly contagious.

CASE IV. R. B. G., a forty year old physician, is illustrative of one of the milder cases. He had the usual three-to-four-day prodromas of headache, malaise, chilliness and fever. He was placed on sulfa thirty-six hours before admission to the hospital, but Figure 7 shows that the

course of the disease was unaffected by its use. The cough remained non-productive. Figure 8 shows that the involvement was chiefly right but there is also some patchy infiltration in the left lower.

CASE V. Mrs. A. V. P. might be called a classical example of atypical pneumonia. For ten days previous to consulting a physician she had a daily temperature elevation from 100°F. to 102°F., headache and marked general malaise. Her husband was ill at the same time with similar complaints. She had a slight dry cough and did not appear acutely ill. Chest examination at first was entirely negative and it remained so until a frothy, grayish sputum began to be expectorated, at which time there were some moist râles in the right upper lobe. Note the extensive involvement in the *x*-ray. (Fig. 9.)

This is the only example among the writer's cases in which the *x*-ray findings are greatly out of proportion to the physical findings. Massive consolidation is not a part of the pathological picture in atypical pneumonia, so naturally widespread dullness, loud tubular breathing indicative of large, solid areas in the lung parenchyma are not found. On the other hand, when carefully sought, the author has been able to demonstrate patchy areas of diminished resonance and crackling or moist râles and the latter

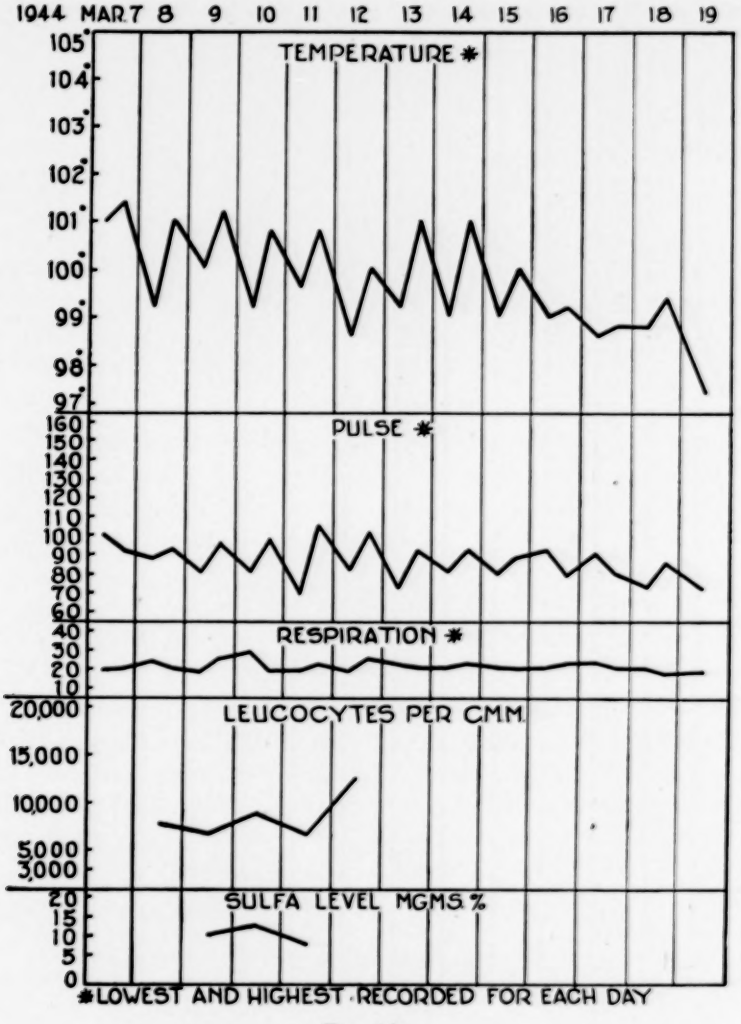

FIG. 13.

is especially true if the sputum is at all productive. Therefore, he believes that the paucity of physical findings has been slightly overemphasized and suggests that much more often than not the area involved may be picked up by physical examination. Figure 10 clearly shows the slow pulse in relation to the temperature, the failure of leukocytosis and the ineffectiveness of the sulfa drug. It was discontinued after five days.

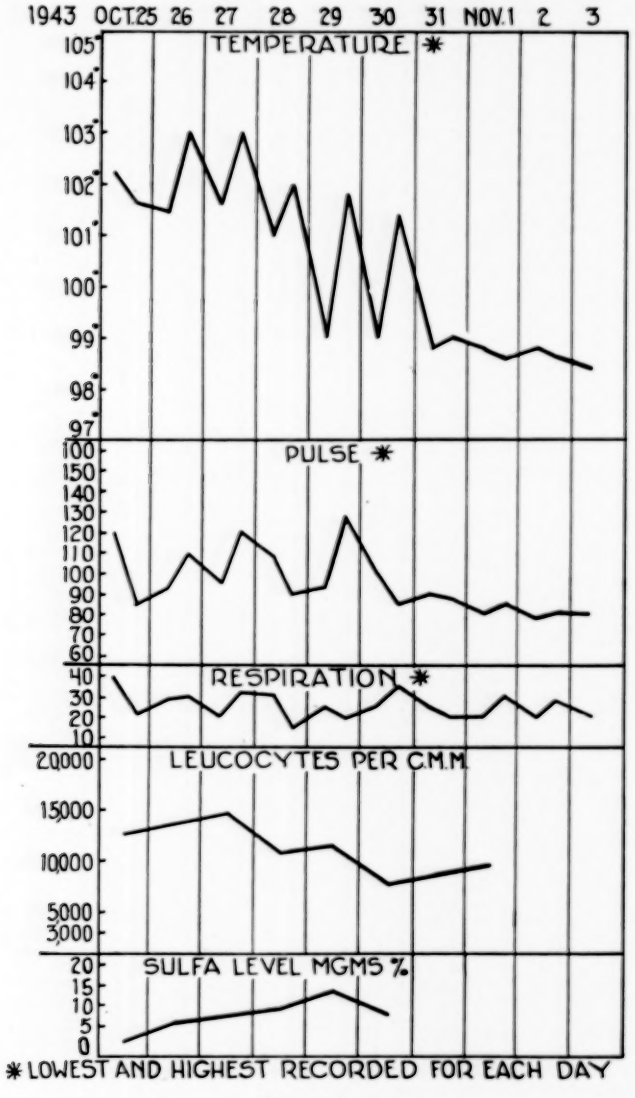

FIG. 14.

CASE VI. W. B., a forty year old patient, had been having chills, fever, headache and a heavy feeling in the upper part of the chest made worse by deep breathing twelve days before coming to the hospital. On the day of admission, March 7, 1944, physical examination of the chest revealed a few sticky râles in the right upper lobe and an *x*-ray plate (Fig. 11) revealed an infiltration in the same area not unlike that caused by the tubercle bacillus. Though he was not very ill and the chest showed nothing positive at physical examination, an *x*-ray (Fig. 12) taken March 13, 1944, disclosed a totally unsuspected involvement of the left lower lobe, while the patch in the right upper lobe had cleared. Six days later he was clinically well. (Fig. 13.)

FIG. 15. Case VII.

CASE VII. J. M. C. suffered with malaise, headache, dry cough, chills, sweats, fever and pain in the chest made worse by deep inspiration for one week previous to admission to the hospital. These symptoms were unrelieved by bed rest and sulfathiazole; and, as Figure 14 illustrates, continuation of the drug (sulfadiazine was also tried) had no appreciable effect on the course of the disease. The cough finally became productive of a grayish-yellow sputum devoid of organisms which could be cultured or typed. There was dullness in the left base and diminished breath tones; a few moist râles developed but there was no bronchial breathing. (Fig. 15.) Twelve days after discharge, this patient developed a sterile effusion in the left base which contained 1,200 white blood cells per c. mm. Three weeks later the chest was entirely clear without further intervention, but about this time he developed a thrombophlebitis which incapacitated him for an additional three weeks. This clearly shows that complications of a distressing nature can follow virus pneumonia and its course is not always "benign."

CASE VIII. W. O., age thirty-five, represents the most virulent example of virus pneumonia the writer has seen. His course was probably intensified by mitral stenosis which complicated the picture; but the widespread involvement, toxemia, marked cyanosis (heliotrope in character), failure to respond to any attempt at therapy and, finally, the many untoward reactions to the sulfa drug (fever, enormous splenomegaly—hard and palpable to umbilicus—urticarial and purpuric skin rashes and marked leukocytosis up to 25,000) made this a very interesting study in what should not be done for virus pneumonia. It should be especially noted that the fever ceased and clinical recovery began when the sulfa drug was discontinued. (Fig. 16.) Figure 17, taken August 24, 1942, shows the typical cardiac silhouette of mitral stenosis and extensive pneumonic involvement of the entire left side. A week later, August 31, 1942, Figure 18 shows slight resolution of the original area with a new one in the left upper lobe and very marked infiltration of the entire right lung. All this had happened while the sulfa level was adequate. Figure 19, taken September 7, 1942, shows considerable clearing of the chest, but the patient by this time was desperately ill from the sulfa drug. He finally recovered.

CONCLUSIONS

1. Virus pneumonia is a highly communicable disease.

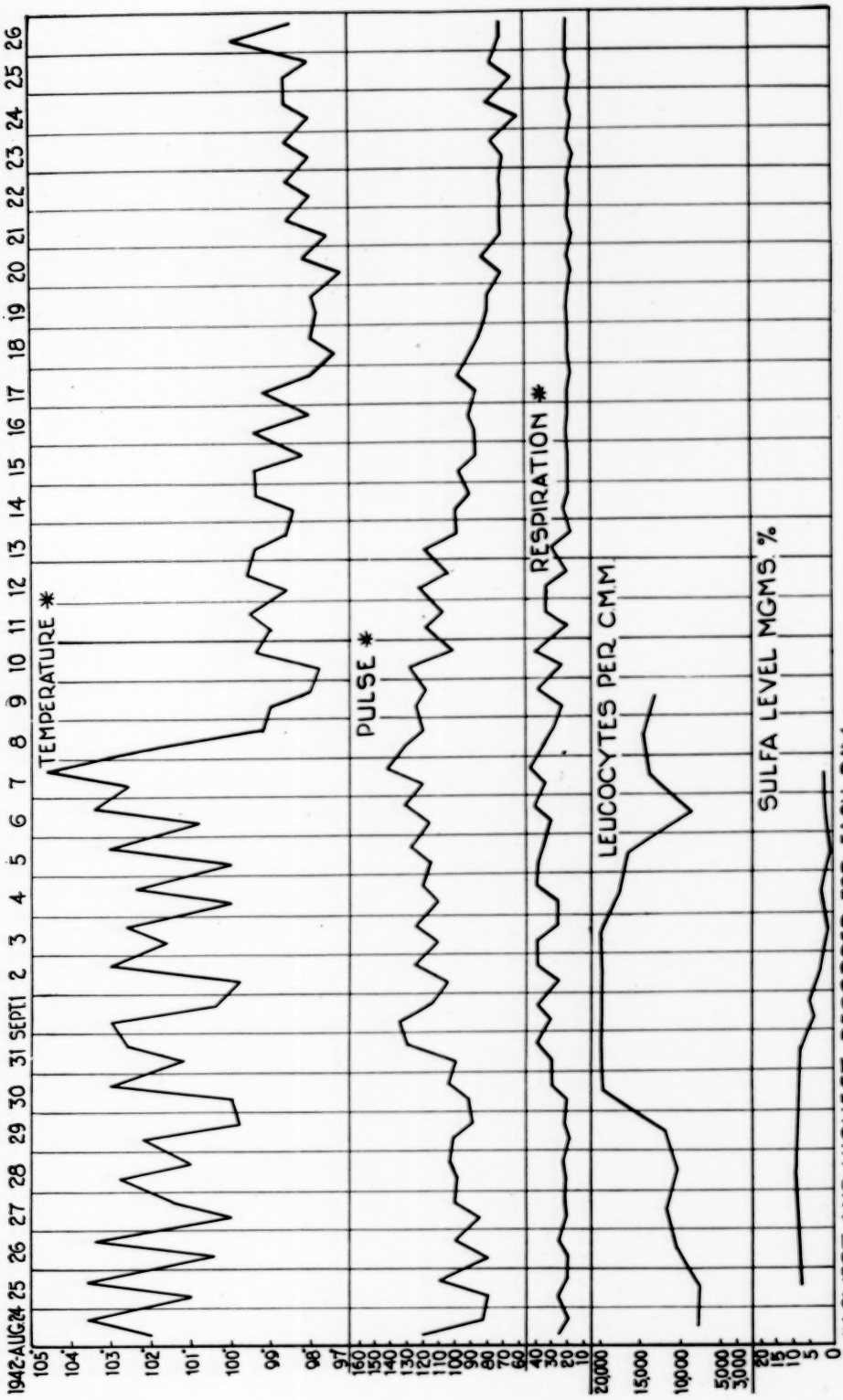
1942-AUG 24 25 26 27 28 29 30 31 SEPT 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26
TEMPERATURE *
105 104 103 102 101 100 99 98 97
PULSE *
160 150 140 130 120 110 100 90 80 70 60
RESPIRATION *
40 30 20 10
LEUCOCYTES PER CMM
20,000 15,000 10,000 5,000 3,000
SULFA LEVEL MGMS. %
20 15 10 5 0
*LOWEST AND HIGHEST RECORDED FOR EACH DAY

FIG. 16.

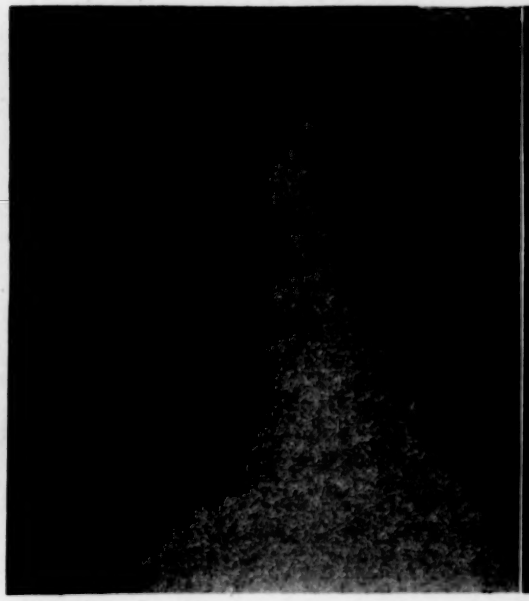

FIG. 17. Note the extensive pneumonic infiltration fanning out from the left hilum and extending into both upper and lower lobes, also the cardiac silhouette of mitral stenosis.

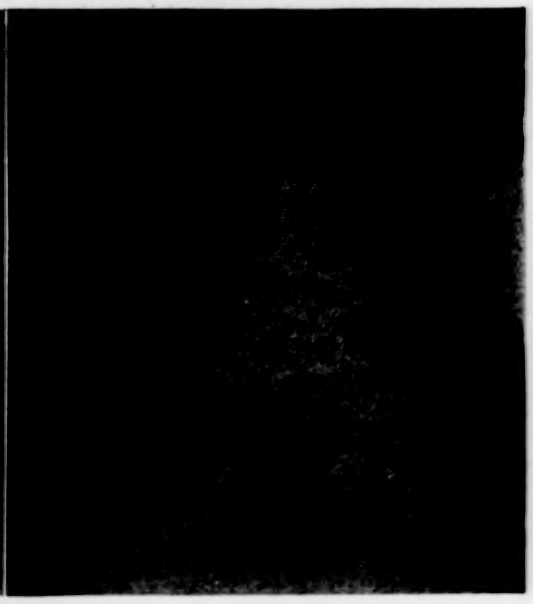

FIG. 18. Case VIII several days after film shown in Figure 17. This plate demonstrates slight resolution in the left lung and massive spread to the entire right lung.

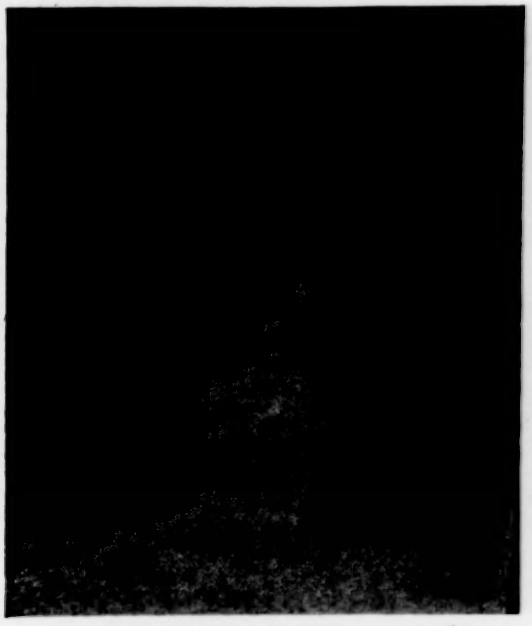

FIG. 19. This is the third film on Case VIII at which time his chest was clearing rapidly but the patient was nearly moribund from sulfa drugs.

2. Its course may be anything but "benign."

3. The disproportion between physical findings and roentgen findings has been overemphasized.

4. The ineffectiveness of sulfa therapy was repeatedly demonstrated and in one instance a near fatality followed persistence in its use.

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Medical Clinic
4212 N. E. Broadway

Review

Recent Advances in the Diagnosis of Human Viral Diseases*

HILARY KOPROWSKI, M.D.

PEARL RIVER, NEW YORK

NOT so many years ago, viruses and viral diseases still presented problems difficult if not impossible to solve by the usual laboratory technics. However, the accumulated evidence of the past two decades indicates that viral diseases follow certain well established patterns in which, to be sure, deviations from normal may occur as frequently or as rarely as in diseases caused by bacteria, fungi and other parasites. Although it does not seem likely that the diagnostic methods for viral diseases will become as simple as those for bacterial infections, numerous tools which facilitate diagnosis do exist. The following summary of such procedures has been written with the hope that it will stimulate some of the physicians hitherto overwhelmed by the perplexities of virology to face and explore the difficulties presented by a case of suspected viral etiology.

It is not the purpose of this review to describe and evaluate all the viral diagnostic procedures. The advance in virology has been so rapid, and the accumulation of literature in the field of diagnosis so great, that it is impossible to outline even briefly all of the recent developments. Therefore, the scope of this paper will be limited to the description of selected procedures which have proved of value in the diagnosis of viral diseases, and for convenience of presentation will be discussed under the following headings: (1) Isolation of the virus, (2) dermal sensitivity tests, (3) serologic tests and (4) diagnosis based on ecology of the disease.

ISOLATION OF THE VIRUS

By far the most important diagnostic technic, both in viral and in bacterial diseases, is the isolation from the patient of the causative agent. Existing diagnostic procedures are time-consuming and consequently in some cases furnish only a retrospective diagnosis, and they require fair-sized diagnostic laboratories with adequate facilities and special equipment. In spite of these disadvantages, no effort should be spared since success in establishing a diagnosis often depends upon isolation of the virus.

Due consideration should be given to the possibility of the existence of virus carriers.[1] Only recently Meyer and Eddie[2] reported a case of a convalescent carrier who had harbored the psittacosis virus for eight years. Thus it is possible that one may isolate from a sick individual a virus which may have been dormant and only concomitant to another agent causing the diseased state. This occurred when Flexner and Amoss[3] isolated a strain of herpes virus from a luetic

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patient who presented no signs of disease other than those of syphilitic infection. However, such instances are probably seldom encountered and fortunately certain serologic procedures to be mentioned later can often resolve such complications.

The type of specimen to be collected from the patient presents another problem for the physicians or laboratory workers who attempt to diagnose the disease by isolation of the virus. In making the selection, the tissue tropism of the suspected causative agent should guide the investigator. In most cases presenting involvement of the central nervous system, blood and spinal fluid may be used. In poliomyelitis, however, fecal material has been considered the best potential source of the virus. In dermal diseases of probable viral etiology, material obtained from skin lesions also may be tested for the presence of the causative agent. Sputum in general has been found a good source of virus in diseases involving the respiratory system, such as psittacosis[2] and other pneumotropic diseases of psittacosis-like etiology[4,5] and the atypical pneumonia group.[6] In cases in which the clinical syndrome indicates the presence of influenza virus, throat washings have been generally employed as test material.

However, in the past the presence of concomitant bacteria in throat washings was a serious drawback in the attempt to isolate the virus by the most effective and simplest method, that is by inoculation of the material into the amniotic cavity of developing chick embryos.[7,8] Because of bacterial contaminants, death of the embryo often occurred before elapse of the period necessary for multiplication of the virus. Introduction of sulfa drugs and of antibiotics helped to overcome this obstacle. For instance, by simultaneous inoculation of penicillin into the amniotic cavity, Hirst[9] isolated the influenza virus from untreated throat washings and prevented bacterial invasion of the embryo. Burnet and Stone[10] found the use of sulfadiazine solution equally effective, and McKee and Hale[11] employed streptomycin for the same purpose. The bacteriostatic action of antibiotics has been useful in the isolation of agents other than that of influenza, for example, of mumps virus from infected saliva.[12] Hodges[13] was able by simultaneous administration of combined solutions of streptomycin and penicillin to combat bacterial growth in chick embryos inoculated with fecal suspensions.

However, in most cases suspected of viral etiology the blood of the patient probably represents one of the best potential sources of the virus. The literature dealing with isolation of viruses from the blood or sera of patients is too extensive to be cited here but the following factors should be considered when isolation of a virus from the blood is being attempted:

1. Blood should be drawn as soon as possible after the onset of illness. The rise in circulating homologous antibodies during the later stages of the disease may cause the disappearance of the virus from the blood stream or, by the simultaneous introduction of immune bodies, may hinder isolation of the virus in the experimental animals.

2. Failure to isolate a particular virus from the blood of patient in a given disease does not necessarily imply that a virus cannot be isolated from the blood in other cases of similar etiology. Whereas in poliomyelitis the virus has been isolated on several occasions from nasopharyngeal swabs, oropharyngeal washings[14] and stools of patients,[15] as well as of contacts,[16] in only one of 111 samples tested had the virus been found in the blood.[17] Nevertheless, by means of blind passages in mice our laboratory has succeeded in isolating a virus from the serum of a mild case of poliomyelitis. This virus was neutralized by convalescent serum of the patient, and subsequent tests

showed that it bore the characteristics of poliomyelitis virus.[18]

After the material is collected with due precautions for sterility, the question arises how to handle it. Should it be delivered to the nearest diagnostic laboratory, or should it be inoculated immediately into a presumably susceptible host at the "bedside" of the patient or at the physician's office? In rural sections, this question is of importance. Should the physician object to bringing animals to his office or to the home of the patient, he can avail himself of two other procedures. One is the technic of inoculation into a developing chick embryo, which is simple enough to permit its application without laboratory facilities,[19] and the other is the use of previously prepared tissue culture flasks.[20] However, as soon as the primary inoculation is made by the physician, the inoculated host or medium should be delivered, together with samples of the original specimen, to the nearest viral diagnostic laboratory for the proper testing. Should delay occur, the original material as well as the tissue harvested from the experimental animal host should be placed in a dry-ice unit, if available, or in the freezing compartment of an ordinary refrigerator. During transit the material should be kept properly chil'ed.

There are three accepted methods for primary isolation of viruses: animal inoculation, chick embryo inoculation and the addition of the infected material to tissue cultures. The practicability of the latter technic in the field has not been sufficiently tested as yet and except for the primary isolation of epidemic kerato-conjunctivitis virus in tissue culture,[21] no new developments have been reported. This leaves animals and chick embryos as the most widely employed hosts for primary isolation of viral pathogens.

The results of inoculation in laboratory animals may help not only in establishing the causative agent in an experimental host but, depending on the host range of the virus and the susceptibility of the animal to different routes of inoculation, may also aid in establishing the diagnosis. Space does not permit discussion of the host range of different viral agents but brief mention will be made of a method by which the response of the mouse may serve to identify the virus among the so-called neurotropic viruses.[22] Let us assume that a group of twenty-eight-day old mice, and another group of fourteen-day old mice, are inoculated with the same material by a parenteral route. If mice in both age groups succumb to infection, one of the equine encephalomyelitis viruses was probably present in the inoculum. However, if the twenty-eight-day old mice survive and the fourteen-day old mice succumb, either St. Louis or Japanese B encephalitis virus may be present.[22] The above example, of course, is hypothetical and greatly simplified. However, by means of correlation of data relating to age of animals, mortality ratio and average survival time, the pathogenic properties of the unknown agent may be so similar to those of a recognized virus that a diagnosis may be postulated with considerable accuracy. For instance, on the basis of these factors it was shown that the St. Louis encephalitis virus was the causative agent in a fatal case of encephalitis recently reported in California.[23]

Formerly, primary isolation of virus in experimental animals often failed because of low concentration of the virus in the original inoculum. Today this is overcome either by concentration of the virus in the original inoculum by Sharples centrifugation,[24] as can be done with poliomyelitis virus in stools and sewage, or by the so-called blind passage technic. The rationale of the latter method is based on the assumption that multiplication of the infectious agent in the initial host is of such a low

order that no apparent clinical signs of the disease are elicited. However, if the animal is sacrificed and the presumably infected tissue passed into another host of the same species, multiplication of the virus in the second-passage host may be rapid enough to educe perceptible signs of illness. During the recent outbreak of Q fever in the United States, the causative agent was isolated from human serum by blind passages in dilute brown agouti mice;[25] the above mentioned isolation of poliomyelitis virus[18] was also attained by the blind passage technic. Moreover, if the serum already contains antibodies, it is possible that by blind passages in laboratory animals the viral agent may be more easily "divorced" from the antibodies and thus an experimental infection in animals be established. It is highly recommended that an adequate portion of serum sample be set aside for the comparative serologic tests, which will be described later. About 20 to 25 ml. of blood obtained during the acute phase of illness should suffice to cover all requirements.

The chick embryo technic has been employed for the isolation of influenza virus,[7,8,26] for herpes virus from penicillin-treated sputum of gingivostomatitis cases and, as already mentioned, for mumps virus.[12] Those interested in the advantages and disadvantages of the use of chick embryos and the practical application of different technics are referred to the comprehensive and excellent monograph recently published by Beveridge and Burnet.[28]

After the experimental infection presumably originating from the human source has been established in a laboratory host, the next step is identification of the agent. Methods employed are described under serologic tests.

DERMAL SENSITIVITY TEST

In diseases of bacterial origin, intracutaneous injections of antigen have been chiefly employed to determine the immunologic status of the individual. In the field of viral diseases, the few dermal sensitivity tests developed serve primarily not as diagnostic procedures *per se* but as evaluations of susceptibility to a given viral disease. A notable exception is the modified Frei test in which antigen prepared from yolk sacs infected with the virus of lymphogranuloma venereum elicits a dermal hypersensitivity reaction in infected individuals.[29]

If herpetic infection persists during the lifetime of an individual[30,31] the *Herpes simplex* dermal sensitivity test developed by Nagler[32,33] may be used as a diagnostic procedure. On the basis of results obtained with the test in fifteen adults subject to labial herpes and fifteen non-herpetic individuals,[33] Nagler came to the conclusion that the test is diagnostically specific.

Beveridge and Burnet[34] inoculated adults and children intradermally with influenza A or B virus-infected allantoic fluids to determine their immunologic status. Most of the adults gave positive skin reactions while of thirty-one children only eighteen reacted positively and of these all but one were reported to have had infection with one or the other type of influenza virus.

Enders et al.[35] described a dermal sensitivity test for mumps in which heated parotid glands of infected monkeys constituted the reagent. The experimental results indicated its specific value as a retrospective diagnostic,[35] or as an indicator of an immunologic status following vaccination.[36] Finally, reagents prepared from yolk sacs infected with meningopneumonitis or with psittacosis viruses have been found to produce erythematous skin reactions in rabbits convalescent from meningopneumonitis infections.[37]

While data at present are still rather meager, the dermal sensitivity tests merit further research because of their potential importance as diagnostic procedures. How-

ever, the increasing number of allergic reactions to vaccines of chick embryo origin[38] may diminish their value unless practical means can be found to free the test reagents of chick proteins.

SEROLOGIC TESTS

It has already been pointed out that the procedures for isolation of virus are time-consuming and thus may cause a delayed diagnosis. Serologic tests, if correctly performed, may be of immediate diagnostic value. Parallel tests should be run on two blood samples drawn from the same individual, one drawn during the onset of the illness and the other drawn several days later. Demonstration of antibodies in a single sample of serum, when accompanied by a typical clinical course, may indicate the correct diagnosis, but only a rise in antibody titer constitutes proof. A correct and rapid diagnosis is of particular importance in viral diseases which may occur as latent infections, such as psittacosis in children.[2] Apparently, this viral disease is one of the few that can be cured by sulfadiazine and penicillin therapy,[39] or by penicillin alone.[2, 40, 41, 42] The criteria of "cure," however, should be carefully determined since in penicillin-treated mice the infection becomes latent and the animals become psittacosis carriers.[43, 44] As stressed by Meyer and Eddie,[2] a properly performed complement-fixation test is of great diagnostic value. In one of their penicillin-treated patients the immunity response was prompt, as shown by rise of complement-fixing antibodies. At the end of ten months the antibody titer had diminished considerably and the authors concluded that "the tissues had been largely freed of the viral agents."

In recent years substantial progress has been made in complement-fixation tests for neurotropic viruses. Antigens without anti-complementary action, prepared from infected mouse brains by Casals and Palacios,[45] were used for diagnostic purposes in the study of an encephalitis epidemic which was shown to have been due to the Western equine encephalomyelitis virus.[46]

Until recently the use of antigen prepared from infected mouse brains was handicapped by non-specific fixation in the presence of Wassermann-positive sera. The recently developed technic[47] of preparing lipoid-free antigen by benzene extraction after lyophilization eliminates such false positive reactions. This method has been used successfully in preparing antigens for Eastern and Western equine encephalomyelitis, St. Louis and Japanese B encephalitis,[47] rabies[48] and Colorado tick fever.[49]

Mumps is another viral disease which recently has received greater attention. A typical case of parotitis can be diagnosed easily because of the unmistakable clinical picture but for atypical cases in which involvement of the central nervous system is the only sign of disease diagnostic methods were not available until Enders and his associates[35] developed a specific complement fixation test. Using parotid gland tissue of an infected monkey as antigen, Kane and Enders[50] were able to diagnose cases of meningo-encephalitis in which involvement of the salivary glands was either slight or absent. Since the complement-fixing antibodies appear with regularity and within a short period after onset of the disease, a new diagnostic tool was made available. However, it should be stressed once again that two specimens of blood should be drawn at intervals of one to two weeks[35] for the complement-fixation test in order to establish a rise in antibody titer which may be considered as diagnostic proof.

The complement-fixation test also provided a means for demonstrating the adaptation of mumps virus to the developing chick embryo,[51] and subsequent evaluation of the egg-adapted virus for immunization experiments.[52]

The hemagglutination-inhibition test is even less time-consuming than the complement-fixation test. So far it has been used extensively in immunologic studies on influenza virus. In studies comparing the complement-fixation with the hemagglutination-inhibition test, Dalldorf and Rice[54] obtained similar results with both technics in a state-wide survey of sera collected in New York state. Hemagglutination has been reported with the viruses of mumps[55] and of vaccinia[56] but application of the hemagglutination-inhibition test in these two diseases has not yet been described.

In some neurotropic viral diseases the neutralizing antibodies may appear earlier in the course of the disease than the complement-fixing antibodies. Sabin,[57] in his study of Japanese B encephalitis among military personnel, described four cases in which the presence of neutralizing and the absence of complement-fixing antibodies was demonstrated between the third to seventh days after the onset of illness. However, because of the time-consuming nature of the neutralization test, results often become available during convalescence, or even posthumously in cases of fulminant encephalitides. Because, in general, the neutralizing antibodies appear early in the course of the disease neutralization tests should be performed on two samples of sera to record any rise in antibody titer.[57] The neutralization test, especially if performed by the parenteral route in mice,[58] represents a more sensitive technic than the complement-fixation test when the susceptibility or resistance to a given viral disease is to be determined. In some diseases, e.g., yellow fever, post-vaccinal immunity can be determined only by a neutralization test.

In describing serologic tests in viral diseases, two tests should be mentioned which are used for diagnostic purposes in a disease of unknown but probable viral etiology, that is, in primary atypical pneumonia. These are the cold hemagglutination test[59] and the agglutination test against a non-hemolytic MG streptococcus.[60] Available data on both tests, recently summarized by Horsfall,[61] have shown MG streptococcus agglutination titers of 1:20 or higher in 48.9 per cent, and cold hemagglutinin titers of 1:40 or higher in the sera of 54.4 per cent of patients with primary atypical pneumonia. If the tests are performed on two or more samples of sera from the same patient a rising titer increases the diagnostic significance of the results.[61]

In concluding the description of serologic tests as diagnostic procedures, mention may be made of the precipitation test developed by Olitzki and Bernkopf in infectious hepatitis.[62] Using a cholesterolized alcohol extract of ether-treated spleen or liver tissue, these investigators were able to demonstrate differences in precipitin titers in sera obtained from patients with infectious hepatitis and those ill from some other disease. Much more evidence is needed before this technic can be accepted as a reliable test.

DIAGNOSIS BASED ON THE ECOLOGY OF THE DISEASE

This phase, unfortunately, has received very little attention in the past. Actually, a careful ecological study may furnish clues to diagnosis. This applies in particular to viral infections transmitted from animals to man, or from man to man, by vectors. It is of lesser importance in diseases transmitted by fomites, water or milk. But even in the latter category, as for instance in infectious hepatitis, careful questioning of the patient about association with jaundiced persons, administration of blood or plasma,[63] may reveal data of diagnostic importance.

An example of how ecologic study may lead to isolation of a new pathogen has been furnished recently by a group of

investigators who described rickettsialpox.[64,65,66] Finding a housing development infested with mites and mice where more than eighty cases had occurred, a field laboratory was set up for the study of their rôle in the disease. Apparently identical strains of rickettsia were recovered from a patient ill with rickettsialpox, from blood-sucking mites collected in the house of the patient, and from a mouse bitten by mites.[66]

During the recent occurrence of Q fever in the United States, a diagnostic clue was furnished by the outbreak occurring among live-stock handlers and slaughter-house workers, incriminating cattle as the source of the infectious agent.[67] Lymphocytic choriomeningitis is another viral disease in which ecologic study may help in establishing a diagnosis. Armstrong and Sweet[68] isolated the virus from gray mice caught in houses in which two human cases had occurred. Whereas mosquitoes,[69] ticks[70] and lice[71] have been found infected with the virus, the above report, as well as the one by Farmer and Janeway,[72] incriminates mice chiefly in the ecology of lymphocytic choriomeningitis. A case of involvement of the central nervous system occurring in a mouse-infested building should no doubt be considered a potential case of lymphocytic choriomeningitis but because of the frequent recovery of the virus from mice[73] consideration of some other causative agent should not be excluded.

There is probably no other viral disease in which study of ecologic conditions is of greater importance than in psittacosis and psittacosis-like diseases. In cases of non-bacterial pneumonitis giving a history of contact with psittacine birds, pigeons, canaries, finches, chickens or sea gulls, psittacosis should be suspected.[2] Psittacosis-like agents have also been isolated from laboratory mice, ferrets, cats and kittens.[2] Recently, Pollard[74] found serologic evidence of a psittacosis-like infection among sea gulls, skimmers and willets, and isolated a psittacosis-like agent from the latter species. Dr. Korns, in his discussion of the presentation by Meyer and Eddie,[2] described an ecologic study of psittacosis on Long Island which incriminated ducks as the source of the epidemic, and duck handlers as psittacosis carriers. Of course not every case of non-bacterial pneumonitis is due to the psittacosis virus, yet a physician who is called to treat such a patient should bear the possibility in mind and report a careful "ecologic record" to the nearest viral diagnostic laboratory.

CONCLUSION

A brief review obviously cannot include all the pertinent data on viral diagnostic procedures and a word of caution should therefore be added. There is a tendency to oversimplify these diagnostic procedures, and very often apparently correct conclusions are drawn from false experimental data. In viral diseases the living experimental host is comparable to the differential bacteriologic media. But the resemblance stops at this point. The experimental host, being a living organism, may harbor an agent or agents which may give rise to a "spontaneous" infection at a time when the inoculated material is expected to educe clinical symptoms. Such an occurrence may not only puzzle an inexperienced observer but may also lead to an erroneous diagnosis. If at any time a clinician has any doubt of his ability to interpret the reactions of an experimental animal to an inoculum, it is highly advisable that he immediately forward the original specimen from the patient, together with the experimental host, to the nearest viral diagnostic laboratory.

Better understanding of the nature of viral diseases has been achieved mainly through the effective cooperation of the

clinicians, pathologists, epidemiologists and diagnostic research laboratories. With the continued teamwork of all concerned further developments may be expected.

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Seminar on Thromboembolism

Operative Treatment of Venous Thrombosis in the Lower Limbs

JOHN HOMANS, M.D.

BOSTON, MASSACHUSETTS

BECAUSE the thromboembolic problem is now being attacked with a reasonable hope of success from two seemingly opposed points of view, it is proposed here to evaluate the means of treatment in use today. Historically, efforts to prevent fatal pulmonary embolism go back into the last century. These efforts have been applied chiefly to postoperative thrombosis as its source with the idea of preserving a normal physiologic condition for the circulatory and muscular systems, a plan which is only partly covered by the term "early ambulation." Some ten or fifteen years ago, it seemed that all that could reasonably be expected had been accomplished. It is only since a newer understanding of the origin and course of venous thrombosis in the lower limbs has been gained that further progress has been made. Briefly, this understanding relates to the occurrence of a quiet, reactionless disease beginning below the knees, and to various grades of this process tending toward and often developing into obstructive inflammatory lesions at a higher level. Attention is thus drawn from an end result—phlegmasia alba dolens—to an early, propagating and therefore dangerous stage of thrombosis. It is also drawn to the interrelationship of lower limb thrombosis and serious disabling disease in general, especially heart disease, and to the occurrence of thrombosis in seemingly normal, active individuals. Naturally, treatment attempts to halt and heal the quiet process at the earliest possible moment and to abolish its dangers. To make clear the principles underlying such treatment there is offered here first a summary of the significant aspects of the disease.

Venous thrombosis starts in the calves, feet, thighs and pelvis (in that order). More than 90 per cent of such thrombosis originates below the inguinal ligaments. Its usual cause is anything disabling which enforces life in bed, namely, operation, disease, injury or childbirth. Its incidence, and especially its liability toward pulmonary embolism, increases with age being greatest during the time from fifty to seventy years of age. Unpredictably and without obvious cause it crops up at any period of active life. In a mixed hospital population not more than 25 per cent of thromboembolism is postoperative and 50 per cent is medical, chiefly as a complication of heart disease. From its origin thrombosis tends to progress upward from a single deep vein or group of veins, causing little or no obstruction to the venous return of blood until it fills the main femoral stem. In its early, quiet form or stage it is known as *phlebothrombosis*. From such a process a friable thrombus, or perhaps better a clot, is apt to break off causing pulmonary embolism. Although thrombosis tends toward a late, outspoken, obstructive stage, namely, *thrombophlebitis*, it may heal rapidly without reaching it, persist even for months without reaching it, or cause death by embolism. In fact, the disease

may have from the start a quiet, propagating, reactionless character, or a more outspoken, inflammatory quality. Most thrombosis is bilateral, yet it is almost always more advanced and obstructive in one leg than the other. Thrombosis necessarily leaves the veins it invades functionless by crippling their valves, but not permanently obstructed since canalization usually occurs. Thrombosis is found, if carefully sought, in about 50 per cent of all autopsies, the greater proportion being terminal, indicating merely the effect of enfeeblement, venous stasis and confinement to bed. Unless prevented, thrombosis occurs in about 1 to 2 per cent of all "surgical" cases; pulmonary embolism of some degree occurs in about 50 per cent of all "surgical" thromboses, and fatal embolism in about 20 per cent of such thromboses. Although some individuals are, for reasons unknown, more liable to thrombosis than others, many of those in whom thrombosis has become established become increasingly thrombophilic—a few almost uncontrollably so.

Pulmonary embolism shows itself in an embolic phase and as infarction. Embolism is suggested by an attack (otherwise unaccountable) of rapid or difficult breathing, of angina-like distress, of syncope (reflex circulatory failure) or of right-sided heart embarrassment. To such disorders, electrocardiographic evidence may offer support. Infarction is indicated by thoracic pain, cough and hemoptysis, and may follow symptoms of embolism or come from a clear sky. In the presence of congestive heart failure, hemoptysis is almost pathognomonic. But it should be recognized that pulmonary embolism may arise from thrombosis in the right heart as well as from the lower limbs. Infarction is best recognized in a thorough, out-of-bed, *x*-ray examination of the thorax.

The diagnosis of thrombosis may be inferred from the discovery of pulmonary embolism, even in the absence of local signs in the lower limbs. It is strongly suggested by an elevation of pulse, temperature and respiration, best seen against a level background—an elevation which may perhaps be accounted for by "preclinical" pulmonary infarction. Local signs in the legs include increased muscular firmness of the calf or actual irritability of the great posterior muscles. Even slight enlargement is significant but edema, cyanosis, tenderness or actual pain are relatively late signs. All signs lag behind the progress of the disease in patients fully confined to bed.

Thrombophlebitis (phlegmasia alba dolens) not only obstructs the femoral and more or less of the iliac veins, together with a variable number of collaterals, but reflexly occasions constriction of the finer blood vessels causing edema of the whole limb and occasionally constrictions of the larger arteries (axon reflex or local effect). The diffuse peripheral vasoconstriction is often released by sympathetic paralysis (lumbar sympathetic block) and by emptying the vein of thrombus. The most favorable effects of treatment are secured before thrombophlebitis has existed for many days. Embolism is rare but cannot be ignored. Loss of its valves and subsequent loss of function in the femoral system (no valves are found in the external or common iliacs) cause most of the bad late results of thrombosis. These are edema of the limb and the development of fibrosis and ulceration in the lower leg. Secondary disablement of lymph drainage is a contributing factor. Pain complexes and secondary varicosity also occur. Veins once thrombosed and canalized are liable to recurrent thrombosis but not necessarily to embolism.

TREATMENT

Though thromboembolism has usually been regarded primarily as a surgical and obstetrical accident, it has actually, as already indicated, as great medical as surgi-

cal significance. Yet so much of the thromboembolism of cardiac and other serious disease is *terminal* that its exact rôle in the morbidity and mortality of a medical service is exceedingly difficult to determine. The operative and chemical treatment of venous thrombosis must take into account this aspect of the problem. In presenting the operative side, I shall indicate very briefly my understanding of the relative therapeutic value of anticoagulant therapy as well as the circumstances under which the two may properly be combined.

Prophylactic Operative Treatment. This has been carried out consistently for several years by Dr. Arthur W. Allen, Dr. Robert R. Linton and their associates[1,2,3] at the Massachusetts General Hospital. The procedure is confined, for all practical purposes, to surgical patients of fifty years and over, subjected to operation in one or more stages for cancer and other serious abdominal, pelvic and thoracic diseases. Because of the frequency of thromboembolism as a complication of fractures of the upper femur and of amputations for arterial disease of the legs, these two categories are included. Some few cardiacs have also been subjected to similar prophylaxis.

Bilateral ligation of the femoral vein distal to and as close as possible to the profunda branch is the procedure used. In skillful, trained hands, the ligation may be combined with the underlying major surgical operation. If not so combined, it is separately performed under a local infiltration anesthetic. Dr. Allen and his associates report the results of 521 such operations to October 1, 1946. Among 458 patients, sixty-five years and over, there occurred one fatal embolism, a relatively small number of thromboses and very few unpleasant after-effects (less edema, etc.) than follows definitive treatment of established thrombosis. Such prophylactic treatment fails, of course, to cover the entire field, since considerable thrombosis (18.5 per cent) occurs in the fifth decade, and it ignores the rare thrombosis of pelvic origin. But since it has seemed impracticable to include patients of all ages down to forty, relegation of those in the younger group* to prophylactic anticoagulant therapy, or to definitive treatment as thrombosis arises, is obviously reasonable.

There is no proof from available statistics that prophylactic treatment with either heparin or dicumarol offers superior protection for the dangerous group in question. There are reports from the Mayo Clinic (Barker et al.),[4] from Murray[5] and from Crafoord[6] and others (Sweden) showing 100 per cent prophylactic postoperative protection by the anticoagulants, but none covers the concentrated, difficult field just mentioned. The same is probably true of gynecological surgery in which comparative figures should soon be available. Although they are not dealing with the problem of prophylaxis, Evans and Boller,[7] in their recent study of fatal embolism at the Lahey Clinic, point out that though intensive postoperative observation, in preparation for anticoagulant therapy of such thromboembolic disease as may be discovered and treated, has lowered still further the already low figures of fatal pulmonary embolism in that clinic, a little group remains (forty-eight in 45,000 major surgical operations from 1940 to 1946) as a problem. In some instances (my comment), routine anticoagulant prophylaxis could hardly have been used and surgical prophylaxis would have been desirable, but to apply prophy-

* I understand that the low age for prophylactic ligation, in connection with a limited variety of operations, is now fifty years. According to Allen, Linton and Donaldson,[1] thrombosis was noted in their control series as follows:

Age	Percentage	
40–50	18.5	
50–60	25.3	61.3
60–70	22.9	
70–80	13.1	

lactic bilateral femoral vein ligation to thousands of patients to save only the ten to twenty whose causal thrombosis could not otherwise have been controlled would seem to be carrying surgery pretty far.

Finally, prophylactic bilateral femoral vein ligation must be performed so skillfully as to result in no accidents whatever related to the operation *per se*. Like anticoagulant therapy, it actually attempts to save so very few that it must injure none. That such can be accomplished in any but specially organized clinics, I very much doubt.

DEFINITIVE TREATMENT

Femoral Vein Ligation. Let it be agreed that a diagnosis of venous thrombosis in one or both lower limbs, whether or not pulmonary embolism has occurred, calls for definitive treatment by vein interruption or anticoagulant therapy. The unavailability of dicumarol or heparin, and especially the unavailability of laboratory tests required for their use, serious disease of liver and kidneys, ulceration within the stomach or intestine, and any hemorrhagic disorder (though such does not seem to threaten thrombosis) may be considered contraindications for anticoagulant therapy and therefore indications for ligation. Once venous thrombosis is diagnosed, persistence of conditions threatening thromboembolism, such as two-stage operations, long confinement to bed by fractures and other injuries, and debility due to diseases requiring a continuous reclining position, are counted positive indications for surgical vein interruption.

The simplest surgical procedure is ligation or section of the femoral vein. The operation must be bilateral. The level at which interruption is to be performed is the debatable consideration. Just proximal to the profunda branch, but distal to the saphenous opening, ligation is most effective in preventing embolism, but this point is a "bottle-neck" and if thrombosis has already involved many collaterals in the thigh a serious degree of stasis and edema will follow. There may even occur an *immediate* serious venous congestion, causing local damage to the limb and some degree of shock. Yet if the femoral vein is ligated distal to the profunda, leaving this great branch open, fatal embolism from this source will occasionally and unpredictably occur. Even a very early lower leg thrombosis is not necessarily controlled by a distal (superficial femoral) ligation. For all that, many proponents of operative treatment prefer the ligation distal to the profunda to that of the common femoral vein, even when they have been obliged to extract soft thrombus by suction from the common femoral and iliac veins.

As to the above problem, I offer the following comments: (1) In a good many instances, superficial femoral vein ligation can be reinforced for the few days before bed-life can be abandoned with anticoagulant therapy; (2) if the common femoral level is selected, a very carefully supervised postoperative course—active exercise in periods of depression alternating with exercise and drainage by elevation—will often establish an excellent collateral circulation and minimize edema; (3) though it is true that once thrombosis has occupied the femoral vein this vessel must become functionally useless whether anticoagulant therapy or surgical interruption is employed, sudden operative closure of the femoral "bottle-neck" has seemed to me a little more crippling than treatment by anticoagulants and (4) even though (3) is true, an advanced thrombosis—the individual being increasingly thrombophilic—is better controlled by vein interruption than by anticoagulant therapy. It is fair, then, to say that surgical judgment and familiarity with the behavior of thrombosis under various conditions will govern the level of

the standard vein interruption. Rules are easy to make and hard to keep. In the following paragraphs I will indicate situations requiring special consideration, namely, thrombosis arising in active individuals, thrombosis without pulmonary embolism and thrombosis accompanied by pulmonary embolism.

Thrombosis arising in active individuals at any age offers a very special problem. Some trifling strain or injury may lead to it, even a long airplane trip. Since there is seemingly little excuse for such an event (I have seen it arise "spontaneously" more than once in girls of eighteen to twenty), it may be supposed that the individual is thrombophilic, a matter not demonstrable as a rule by ordinary blood tests. In the older age group, pulmonary embolism, even repeated pulmonary embolism, may occur simulating angina pectoris or coronary disease. Before anticoagulants were available in the early 1930's, I treated all such patients[8,9] by vein interruption. I now believe that early thrombosis, when the process has not yet invaded the femoral vein (the extent of the disease is much easier to recognize in ambulatory than bed patients) should be given anticoagulant therapy, preferably with dicumarol. I have even permitted one patient, a doctor, to be ambulatory under dicumarol treatment, since he was able to secure daily blood tests of the prothrombin level. For more chronic and advanced disease of this sort, vein interruption should be used, either superficial femoral vein ligation or, if the disease is clearly unilateral, ligation of the common iliac vein, an operation which I have previously described[10,11] and will presently discuss. In connection with either of these procedures, blood studies, perhaps after DeTakat's[12] suggestion of a test reaction to heparin, are indicated; and should the blood appear thrombophilic, anticoagulant therapy may be combined with surgery during the few days in which the patient is becoming fully ambulatory.

Thrombosis without pulmonary embolism recognized in patients recently subjected to major surgery, in those convalescent from such an illness as pneumonia and in many of those suffering from cardiac decompensation and from coronary occlusion, should receive anticoagulant therapy. I group these patients together since they are likely to offer the opportunity to use anticoagulants *for a limited time while the individual is returning to an active life*. If possible, I would exclude from this group patients of the bad risk sort unlikely to return soon to normal life and therefore persistently liable to thrombosis, as already explained. This is perhaps the ideal way to use anticoagulants as indicated by Bauer,[13] Jorpes[14,15] and the Swedish school in general.

Thrombosis accompanied by pulmonary embolism is preferably treated by vein interruption. Bilateral femoral vein ligation is to be used. These patients, in whom thrombosis is presumably well established, may already be very troublesome problems for anticoagulant therapy. Dosage will usually be difficult to establish and further embolism is likely to be fatal. It may also happen that ambulation must be delayed considerably in which case vein interruption will have its greatest authority. As a rule these are bad risk patients. In most instances of this sort, the thrombosis will clearly be present in the legs and can be regarded as bilateral, though its extent toward the heart may be very difficult to determine. Sometimes, however, there will be no way of excluding a pelvic origin for thrombosis as in many gynecologic and prostatic cases. Then the question will arise whether to explore both femoral veins and suck out such soft thrombus as may be found, or whether to admit that the process can be controlled surgically only by a vena caval ligation. If the femoral vein exploration is

used, it should probably be supported by anticoagulant treatment in fear of further immediate embolism from any thrombus left in the great iliac veins. Such anticoagulant treatment may also be indicated in support of vein interruption in cardiac cases because of uncertainty whether embolism is coming from the legs or from the right heart.

COMMON ILIAC VEIN LIGATION

When a chronic or recurrent thrombosis appears to be *unilateral*, as in a considerable number of instances of old thrombophlebitis and especially when embolism from such a process is proved or suspected, common iliac ligation[10,11] offers very decided advantages. The operation is acknowledged to be more difficult than femoral vein ligation and requires a general anesthetic. Sometimes the vein is friable and dangerous to handle. But the collateral circulation is vastly more abundant than when the common femoral vein is interrupted. Indeed, one can be sure that the venous return will be improved by the procedure. Bancroft[16,17] has made considerable use of it. In my own experience of fifteen such interruptions, further embolism has been prevented but the operation does not fully protect against an occasional recurrence of thrombosis. In only one case, however, has this been true.

VENA CAVAL INTERRUPTION

There is now available a number of reports of this procedure sufficient to assay its value and warn of its dangers. When serious embolism has occurred and especially when further embolism must be prevented at all costs, the operation offers the surest protection. Under these circumstances it should be preferred to a more peripheral interruption in the presence of an ascending bilateral thrombosis of the lower limbs. It may even be used (in the absence of cardiac disease as a possible source) when the origin of embolism is merely presumed though not proved to be in the pelvis or lower limbs. But if a pelvic (uterine or ovarian) origin is suspected, the ovarian veins as well as the vena cava must be ligated (Collins, Jones and Nelson).[18]

To those, like Murray,[5] who appear convinced that anticoagulant therapy will always control thrombosis and prevent fatal embolism, even after warning and after nearly fatal embolisms have already occurred, vena caval ligation must seem an unnecessary and dangerous surgical venture. But under the conditions outlined in the preceding paragraph, the operation in skilled hands is entirely reasonable and sometimes inevitable. Wider indications are noted by Moses[19] and more recently by Veal, Hussey and Barnes.[20] The resulting collateral circulation may be accepted as satisfactory. As to the technical difficulty and danger of the operation, a general anesthetic is required and the vena cava should be approached in such a way as to secure a good anterior view of the great vessel. For any lateral branches encountered are fragile and may be torn by the manipulation required for ligation; in which case, hemorrhage is difficult to control and may well be fatal. Actually, the operation is less disturbing to the very ill patient than one might suppose—far less so than a transperitoneal procedure—so that its proper mortality can be neglected. The re-education of the return circulation requires care but does not offer a serious problem.

I myself regard the operation as a last resort when peripheral ligation or anticoagulant therapy or a combination of both, as sometimes happens, have failed to halt embolism. Even though several series of thirty or more cases have been published from various surgical clinics, the mortality which has followed the operation, though relatively low and mainly attributable to

underlying disease, suggests that the operation has been somewhat overdone.

TREATMENT OF THROMBOPHLEBITIS

The obstructive, often inflammatory phase of thrombosis requires treatment devoted to both venous occlusion and secondary vasospasm. Embolism is a very minor consideration but since an outspoken phlegmasia alba dolens in one leg may carry with it a quiet phlebothrombosis in the other, that aspect of the disease must not be neglected. I have already pointed out that vasoconstriction declares itself mainly in the peripheral arterioles and venules but may provoke, though rarely, a serious persistent spasm of the great artery of the limb, even violent enough in some cases to cause gangrene. Ochsner and deBakey[21,22] have shown how the inflammatory reaction in a segment of vein can call forth reflexes inducing such effects, and how profoundly sympathetic paralysis, even a temporary block with procaine, can favorably affect the state of the swollen painful limb. The vicious circle of venous irritation and reflex sympathetic constriction can actually be broken by emptying the obstructed vein or even by surgically exposing it for some distance, but lumbar sympathetic block, as first suggested by Leriche,[23] is the standard procedure.

Lumbar sympathetic procaine block may be secured by various technics. The main thing is that it should paralyze, if only for fifteen minutes, the lumbar sympathetic chain. Several blocks over a series of days may be required to secure maximal release but even a single one is often extraordinarily efficient. The leg visibly shrinks, the skin wrinkles, the bluish pallor changes to pinkness, comfort is produced and surface veins begin to fill. But because the second leg may be the source of an embolus-threatening process, and because the thrombophlebitis itself may rarely cause embolism, anticoagulant therapy should be used for a week or so, or a superficial femoral vein ligation done on the second leg.

It has been shown that in the early stage of phlegmasia alba dolens (first week) femoral exploration and thrombectomy will have much the same effect as sympathetic block and will greatly shorten the convalescence. If this operation is carried out, the opposite superficial femoral vein can be ligated at the same sitting. A very important contribution of this operation is a permanent interruption of the superficial femoral vein (distal to the profunda). For canalization of the thrombosed vein is so much the rule that serious back pressure and consequent venous congestion of the entire leg often follow healing of thrombophlebitis. Both Buxton and Coller[24,25] and the writer[26] treated the late complications of thrombophlebitis surgically by sectioning the now valveless femoral and saphenous veins. It may be that interruption during the acute state will prevent much future venous stasis, edema and ulceration. Obviously, it should not be performed in the presence of a lymphangitis in the femoral chain of nodes. Nor should any surgical procedure cause neglect of the carefully controlled convalescence, particularly the re-education of the venous return by gradual use of the limb in dependency.

TREATMENT OF THROMBOEMBOLISM IN "MEDICAL" PATIENTS

In 1940, White[27] called attention to "pulmonary embolism and heart disease" and Hampton and Castleman[28] showed by combined roentgenologic and pathologic study at the Massachusetts General Hospital that 60 per cent of fatal embolism was of medical origin—chiefly cardiac—against 40 per cent of a surgical sort. Since then, this side of the subject has received considerable but not yet sufficient recognition. In the description given at the beginning of

this paper, the frequent imitation of coronary occlusion and angina by pulmonary embolism was indicated. But when genuine heart disease exists, particularly congestive failure associated with hypertensive or rheumatic disease or coronary occlusion, it may well happen that a complicating venous thrombosis in the lower limbs and embolism from that source decidedly increase the danger to the patient over and beyond that relating to the cardiac condition itself.

To simplify as far as possible the problem of preventing such thromboembolism, and of treating it when established, one will do well to make very broad rules for diagnosis and treatment, admitting that accurate diagnosis is unattainable and that treatment is based on probabilities. Thus, the majority of those confined to bed by heart disease and kept for many days in a reclining position, with the legs somewhat dependent, relaxed and engorged, will develop thrombosis in their lower limbs, though the terminal quality of much of this thrombosis has already been noted. Such thrombosis may cause pulmonary embolism at any time. The quieter the process, the greater the danger of embolism from it. Edema of the limbs will usually be present whether or not thrombosis exists. Therefore, local muscular signs and actual embolism offer the chief evidence for the diagnosis. Pulmonary infarction is indicated by thoracic pain, hemoptysis and, especially, shadows on the *x*-ray film. Actual proof that any episode of pulmonary infarction is of lower-limb rather than of cardiac origin may be wanting but the percentages very decidedly favor the legs.

The effectiveness of dicumarol in the treatment of certain types of heart disease has been demonstrated by Wright[29] who believes that this anticoagulant can be continued, with proper controls, for long periods. However, the uncertainties of response to this drug, particularly in respect to its assimilation and its action when the liver and kidneys are damaged, indicate the usefulness of vein interruption, at least as an alternative.

It is a good rule then that if, in any instance of heart disease in which confinement to bed for more than a week is expected, embolism is believed to have occurred (from thrombosis clinically evident or presumed to be present in the lower limbs), both common femoral veins should be explored and ligated. When there are actual contraindications for the anticoagulants, such a rule may be counted imperative; otherwise it is a matter for professional experience and judgment to determine. Carlotti, Hardy, Linton and White,[30] in a very informative and thoughtful communication to the American Heart Association, discuss surgical treatment by vein interruption, and I am permitted to indicate the nature of their results. Among 151 cases (1941 to 1945) of heart disease in whom a diagnosis of embolism or infarction was made by any of several methods, sixty patients were subjected to femoral vein section (bilateral since 1943). Seventeen deaths in the group subjected to operation give a mortality of 28.3 per cent, as opposed to 50.7 per cent in a control series of 213 cases. Thirteen failures to prevent embolism (clinical evidence of infarction after operation) included no massive fatal embolisms, and in eleven of the thirteen the superficial rather than the common femoral veins had been divided. The authors have since used only bilateral common femoral vein interruption. Their publication deserves careful study.

COMMENTS

It will have been noted that in presenting the prophylactic and definitive treatment of venous thrombosis in the lower limbs I have made few didactic statements, that I have indicated a personal preference for anticoagulant therapy under a number of

conditions and that I have suggested here and there the advisability of a combined chemicosurgical treatment. Venous thrombosis occurs in the home, in rather primitive hospitals and in well equipped and staffed urban institutions. Moreover, the clinical conditions under which thromboembolism presents itself are many—postoperative, post-traumatic, medical, obstetric—and the disease appears to vary from clinic to clinic, from country to country, and certainly from climate to climate. Until statistics from many sources and on a scale larger than are now available are brought forward to cover strictly comparable groups of patients, it will be impossible to assay the relative value of anticoagulant and surgical treatment. It is my impression at the moment that today's tendency is toward increased use of the anticoagulant drugs—they became available only several years after the value of a vein interruption had become known—with the significant reservation that their use calls for expert knowledge and routine study of the blood. Heparin or dicumarol are particularly indicated in the treatment of acute, single episodes of thromboembolism. Interruption of veins is advantageous when the causes of thromboembolism are persistent or recurrent, or when any further embolism must at all costs be prevented. Both systems, optimistic statements to the contrary notwithstanding, will score tragic failures as well as dramatic successes and clearer indications for treatment than those now available will be made known only gradually.

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Combined Staff Clinics

Smallpox

THESE are stenotyped reports of combined staff clinics of the College of Physicians and Surgeons, Columbia University, and the Presbyterian Hospital. The clinics, designed to integrate basic mechanisms of disease with problems of diagnosis and treatment, are conducted under the auspices of the Department of Medicine. The reports are edited by Dr. Frederick K. Heath.

DR. HARRY M. ROSE: Smallpox is a subject that usually receives little attention in this part of the world. This attitude seems mainly to be the result of the fact that smallpox has virtually disappeared from our communities, together with the common belief that the general level of immunity in our population, produced by prophylactic vaccination, is sufficiently high to prevent any serious recurrence of the disease. Recently, however, smallpox appeared again in New York City. The source of the infection and the circumstances of the outbreak that followed will form a part of this discussion and it will be apparent that a serious epidemic was averted, probably only by the prompt and resourceful measures of control employed by the New York City Department of Health. Although the actual number of cases of smallpox in this outbreak fortunately was small, the public was considerably alarmed and the medical profession was made to realize that the disease still presents many unsolved problems. It is the purpose of this clinic to discuss some of these problems and to summarize the current knowledge of smallpox in the light of our recent experience.

Dr. Kneeland will open the discussion with a consideration of the clinical aspects of smallpox.

DR. YALE KNEELAND, JR.: It is likely that the vast majority of this audience has never seen a patient with smallpox. Indeed, it is a disease to which most of us in normal circumstances never give a thought; we regard ourselves and our own society as completely protected. At some time or other we have skimmed through a textbook description which we can remember but vaguely and we think of the disease—if at all—as something visited on the unenlightened peoples of the earth for their sins, something which can never possibly happen to us. Yet a recent issue of the Army Medical Bulletin* reports twenty-six cases with twelve deaths occurring in presumably immune American troops in Korea; fifty-nine cases with eight deaths in our similarly protected army of occupation in Japan and a secondary epidemic (from this source) taking place in Seattle with forty cases, eight of them fatal. Recently we had the disease in New York.

My own credentials as a clinical lecturer on smallpox are not impressive. True, I have seen a great many cases. But I saw them all in one day, in a fever hospital in the Middle East. This sort of experience does not impart a deep appreciation of any disease as a whole. Nevertheless, it made an indelible impression and has caused me to read about smallpox with avidity.

Now I do not think that any of you should endeavor to memorize all the details of the disease but you can rightly be expected to do two things: to bear it in mind and to have enough schematic notion of what it is like to suspect its presence if it occurs. Let us, therefore, review the classical textbook description and then compare it with some recent experiences in the field. For this pur-

* *Bull. U. S. Army M. Dept.*, 5: 616, 1946.

pose it is convenient to have before our eyes a graphic representation of the typical behavior of smallpox, and I have borrowed an excellent diagram from Dr. Murray Cowie's article in Cecil's Textbook of Medicine to serve this purpose. (Fig. 1.) Be it remarked

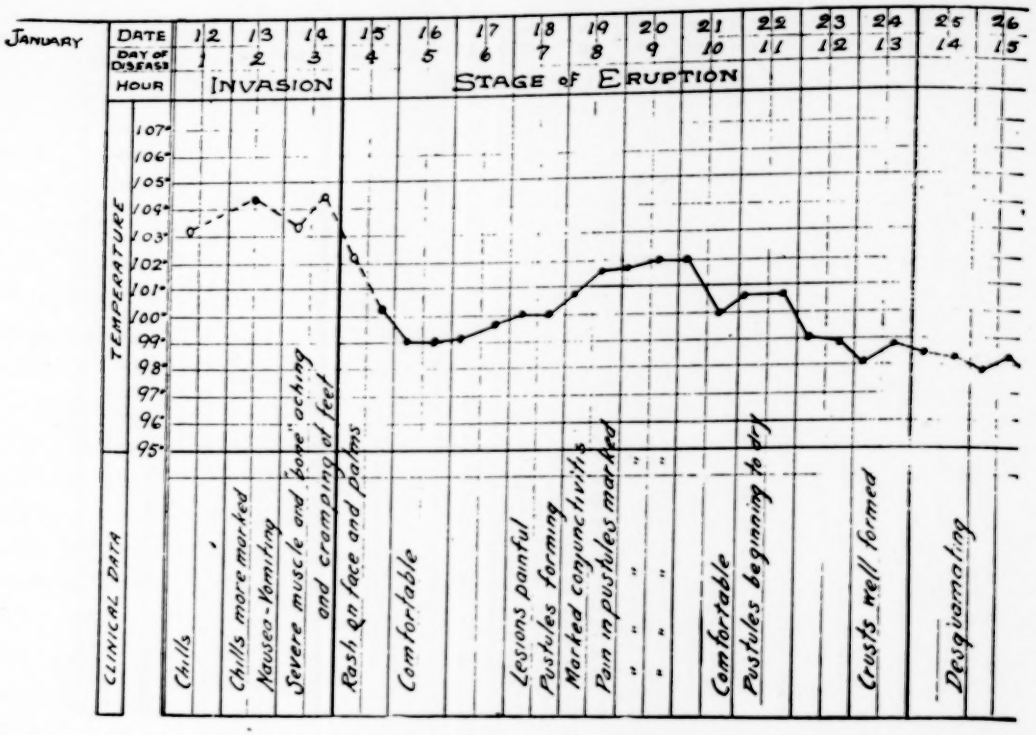


FIG. 1. Typical temperature curve from a case of smallpox, illustrating the secondary rise. (From Cecil's Textbook of Medicine.)

that unmodified virus and rickettsial diseases often tend to run remarkably close to form and smallpox is, therefore, the sort of disease in which a schematic chart is of the most value.

The incubation period is usually around twelve days, although very rarely it may be as long as twenty-one days. The disease begins abruptly and there ensues a period of invasion referred to as the "prodromal fever," which is characterized by chills, marked elevation of temperature, prostration, aching pains and vomiting. The total white count is usually within normal limits. Plainly then, there is nothing to distinguish smallpox at this stage from a variety of other acute infections. Depending on season and geography it will be confused with influenza, typhus, sand fly fever, dengue fever, malaria and a host of others that come readily to mind. During this stage occasional "prodromal rashes," petechial, morbilliform or scarlatiniform, are described but I do not think that we need burden our memory with these. On or about the fourth day, however, the characteristic exanthem of smallpox makes its appearance. It begins as a discrete macular rash but the macules rapidly become papular and have a shotty feel. Coincidently with the rash the temperature falls and the patient feels better.

It is important to remember something about the distribution of the rash. Ordinarily, it appears first on the face; then it rapidly involves the upper extremities, with a preference for their distal portions; the trunk is next involved but usually less strikingly, and lastly the lower extremities become involved where most of the lesions are found below the knee. The palms and

soles are involved. The development of the exanthem is rapid and the phenomenon of "cropping" is not observed. That is to say, most of the lesions will be found in the same stage of development. This, together with the peripheral distribution, and the deeper, more indurated character of the lesion help to differentiate smallpox from varicella.

By about the sixth day of the disease the papules change into vesicles and tend to become umbilicated; by the eighth day their contents become turbid and the stage of pustulation has been reached. With this there is a secondary rise in temperature, an increase in constitutional reaction and often considerable local pain and pruritus. The lesions then begin to dry and crust. By the end of a fortnight the crusts are well formed and adherent and the fever has usually abated. Separation of the crusts and some desquamation then takes place; these processes are complete by the end of a month, leaving behind the permanent, pitted scars of the disease which are so familiar. Incidentally, there is also an enanthem, i.e., the eruption affects buccal, pharyngeal and other mucous membranes where extensive ulcerations may occur.

Smallpox epidemics in the past have varied considerably in severity, and the patient fatality rate of 15 to 45 per cent is a function of the relative predominance of the various clinical types which, in turn, is conditioned by the immunity of the population. The three main clinical types are the *discrete*, in which the lesions are separated and may be scanty and the mortality is very low, the *confluent* (Fig. 2, photograph I took in the Fever Hospital in Cairo) in which the fatality rate may approach 50 per cent, and the *hemorrhagic*. The latter is described as two types: "Purpura variolosa" or "black smallpox," in which there is early and extensive purpura and death is the rule; and "Variola hemorrhagica pustulosa" in which bleeding is limited to the lesions themselves

FIG. 2. Typical type of rash in confluent smallpox.

and the mortality is somewhat lower. Death may occur as a result of profound intoxication in severe smallpox, that is to say, owing to overwhelming virus infection itself. In untreated patients it may also occur from concomitant bronchopneumonia or septic complications.

So much for the schematic description of the disease, the salient features of which every physician should bear in mind. Let us turn now to a recent clinical experience with this historic disease. Illingworth and Oliver* have written an excellent description of one hundred patients with smallpox in the British military personnel in the Middle East. Of these, 96 per cent had been vaccinated, 70 per cent within two years of the epidemic. In other words it was the sort of population we might expect to deal with in an epidemic in this country. In spite of the vaccinations there were fourteen deaths. However, no doubt because of vaccination, they classified 54 per cent of their patients as "modified." I shall return to them a little later but first, in regard to *unmodified smallpox*, it is of interest that the authors found that it conformed closely to the classical description I have outlined above. They did note that headache was a more impressive symptom during the prodromal fever than backache (so frequently emphasized in the

* ILLINGWORTH, R. S. and OLIVER, W. A. *Lancet*, 2: 681, 1944.

literature) but in other respects the pattern ran true to form. The spleen was palpable in about half their patients and a leukocytosis early in the disease was associated with the hemorrhagic type. In non-hemorrhagic patients the count was usually around 8,000, with a tendency to rise late in the disease, at which time immature white cells and a reduction of platelets were noted.

The striking feature of the *modified cases* was the shortening of the prodromal fever. Sometimes these patients presented themselves with a vesicular eruption. Other patients might develop a vesicular rash after a day or two of fever, the vesicles then either maturing rapidly into the pustular form or aborting. It is quite obvious that in such patients the resemblance to chickenpox was very close indeed. The main clinical points of differentiation which the authors found of value were the presence of shotty nodules in the palms and the involvement of the palate and conjunctivae. These are characteristic of smallpox. Nevertheless, the two diseases may be impossible to separate on purely clinical grounds. Dr. Cox will probably tell you about the technic of serologic diagnosis and of virus identification. These methods unfortunately involve a great deal of time and, of course, the services of a first-rate virus laboratory. A quick test of some sort would be of obvious value in the field. Such a one has been described by Van Rooyen and Illingworth.* This consists in the demonstration of elementary bodies in specially stained smears from the lesions. Its great advantage lies in the fact that it can be done very quickly. Unfortunately, it too requires an experienced and highly trained technician but the results would appear to justify such training. Van Rooyen and Illingworth obtained positive results in forty-seven of fifty patients studied, in half of whom the clinical diagnosis had not yet been established, and there were no false positives.

While the diagnosis of typical florid smallpox is not difficult, I do not wish to leave in your minds the impression that it is an easy diagnosis to make in all cases. Far from it. I have already mentioned the difficulty in distinguishing it from varicella, particularly when the smallpox is "modified." The onset of chickenpox, the distribution of the eruption, its characteristic evolution, the fever curve, etc., differentiate it from unmodified smallpox. Many of these differences vanish when the smallpox occurs in a partially immune individual, and the remaining differences are too subtle for full clinical reliance. Apart from varicella there are other sources of confusion. I have indicated that there is nothing characteristic about the prodromal fever. In the early stages of the eruption it must be distinguished from scarlet fever and measles. When seen in the pustular stage it may be confused with any pustular dermatosis. To repeat, differential diagnosis is difficult and may be impossible but the first necessity is to realize that smallpox exists, to keep it in the back of one's mind and to remember some of its characteristic features.

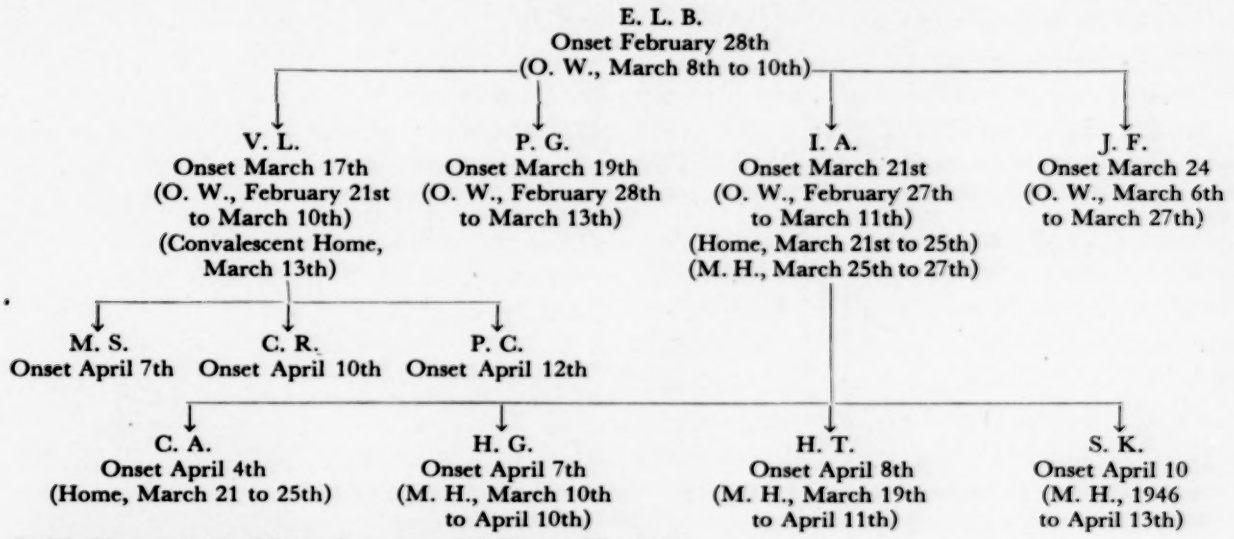
Dr. Rose: Dr. Kneeland has given a lucid account of the classical clinical features of smallpox as it occurs in the nonimmune human subject. He has also pointed out that the classical picture of smallpox may be modified, often as the result of previous vaccination, and that the modified or atypical forms of the disease may be confused clinically with other acute exanthemata, notably chickenpox. We must constantly be alert to the possibility of smallpox in any patient whose signs and symptoms even remotely suggest the disease. Failure to recognize promptly and to isolate an atypical case of smallpox may lead to spread of the disease by extension to nonimmune contacts, as illustrated by the

* Van Rooyen, C. E. and Illingworth, R. S. *Brit. M. J.*, 2: 526, 1944.

recent outbreak of smallpox in New York City. This was initiated by a patient in whom the clinical diagnosis was missed and who was not isolated in a communicable disease hospital until the tenth day of his illness, two days before death. The epidemiologic features of the outbreak and the control measures employed for successfully limiting the spread of the disease will now be discussed by Dr. Morris Greenberg, Acting Director of the Bureau of Preventable Diseases, New York City Department of Health.

TABLE I

SPREAD OF SMALLPOX TO SECONDARY AND TERTIARY CONTACTS IN THE NEW YORK CITY OUTBREAK, 1947



O. W. Observation building—Communicable Disease Hospital
M. H. Municipal Hospital

DR. MORRIS GREENBERG: Prior to the recent outbreak there had not been a case of smallpox developing in the city of New York for more than a generation. The last patient seen in the city was in 1939 when a person arrived with smallpox on a Portuguese boat. He was immediately isolated and no secondary cases occurred.

CASE I. The 1947 outbreak of smallpox could be traced back to the arrival in this city of an American business man, E. L. B., aged fifty, who had lived in Mexico for the past six or seven years. He left Mexico City on February 25, 1947, and traveled by bus to New York City, with several short stops en route, arriving here on March 1st. According to his wife, who accompanied him, he became ill on February 28th. He registered at a midtown hotel on arrival and transacted business until March 5th when he felt too sick to work. He was admitted to a municipal hospital on that day and remained there until March 8th when he was transferred to a communicable disease hospital. He was placed on the first floor of the observation building. He was then quite ill with pustular and hemorrhagic lesions all over his body. He died on March 10th. The possibility of smallpox was considered but a definite diagnosis was not made.

The man had been vaccinated in childhood. His wife was vaccinated in the communicable disease hospital.

The further spread of the disease is delineated in Table I, which summarizes the results of the epidemiologic studies in this outbreak. A more detailed analysis follows.

CASE II. On March 27th, I. A., a

Puerto Rican adult, aged twenty-six, was admitted to the communicable disease hospital. He had previously been admitted to the same hospital on February 27th for mumps and had been placed on the sixth floor of the observation building where he remained until March 11th, when he was discharged as cured. He worked until March 21st, when he became ill with headache and fever and went home. On March 25th, he was admitted to the dermatologic ward of a municipal hospital where he remained until March 27th. Then he was transferred to the communicable disease hospital and placed in isolation. He had a generalized papulo-vesiculo-pustular eruption. Smallpox was suspected and material from the lesions was sent to Dr. Smadel of the Army Medical School. Characteristic growth (on chick embryo) was obtained as well as a positive complement fixation reaction with antismallpox serum. The man had never been vaccinated. Attempts at vaccination in the hospital on two occasions gave no reactions.

Case III. When I. A. was admitted to the isolation building on March 27th, two children were in isolation, P. G., a female, colored, aged twenty-two months, and J. F., male, Puerto Rican, aged two and one-half years. Neither had been vaccinated before. P. G. had been admitted to the same hospital on the first floor of the observation building, for croup, on February 26th and had remained until March 13th. On March 19th, she became ill at home, with fever and rash. Two days later she applied to a local clinic which sent her to the communicable disease hospital. She had a generalized papulovesicular eruption and was placed in isolation. The child did not appear very ill and the vesicular lesions, although present all over the body, including face, palms and soles, contained clear fluid. Material from the vesicles, examined at the same time as that of I. A., gave a characteristic growth on chick embryo and a positive complement fixation reaction was obtained.

Case IV. J. F., the other child, had been on the first floor of the observation building since March 6th for possible whooping cough. On March 24th he developed fever which continued for several days. On March 27th a papulovesicular eruption was seen and the child was transferred to the isolation building. The eruption was never widespread, although lesions were seen on face, palms and soles, and the child was not very sick. However, growth on chick embryo was obtained and also a positive complement fixation reaction. On two occasions this child as well as the previous child were vaccinated in the hospital after their lesions had appeared, but with no success.

Case V. Still another child, who was a contact of the first child, developed smallpox. This was V. L., a colored male, aged four, who had never been vaccinated. He had been admitted to the third floor of the observation ward of the hospital for possible scarlet fever on February 20th and discharged as cured on March 10th. On March 13th he was admitted to a convalescent home upstate. He became ill with fever on March 17th and developed a rash which was diagnosed as smallpox. Three secondary cases occurred in the convalescent home; a white nurse, aged sixty, who had not been vaccinated since childhood; a colored boy, aged five, and a white girl, aged two. Neither of the children had ever been vaccinated.

Case VI. I. A., Case II, had been sick at home from March 21st to March 25th. His wife, C. A., Puerto Rican, aged twenty-six, a primipara of seven months who had never been vaccinated, became ill on April 5th with backache, headache and fever. She was admitted the next day to the isolation building of the communicable disease hospital. At this time she had some maculopapules resembling rose spots on her chest

and one on her face. These developed and spread and within a few days she had a typical smallpox eruption. She had been vaccinated on April 4th and had a good take. She died on April 12th.

CASE VII. As stated above, case II had been admitted to the dermatologic ward of a municipal hospital on March 25th and remained there until March 27th. On the same ward at that time there were three patients who later developed smallpox. One of these was H. G., a colored man, aged forty-three, who had been on the ward under treatment for syphilis since March 10th. He had never been vaccinated. On April 7th he developed fever and headache and on April 10th a papular eruption appeared. He was transferred to the isolation building of the communicable disease hospital the same day. He developed severe confluent smallpox. He was vaccinated on April 9th and had a good take.

CASE VIII. The second man, H. T., white, aged fifty-seven, had never been vaccinated. He had been on the ward since March 19th with lymphoblastoma. He developed fever on April 8th and a rash was noted the same day. It was papular and later became vesicular, spreading until it involved the entire body. He was transferred to the isolation building of the communicable disease hospital on April 10th. He was vaccinated on April 9th and had a good take.

CASE IX. The third individual was S. K., white, aged sixty, who had been vaccinated about forty years before. He had been on the ward with pemphigus since August 6, 1946. He became ill with fever on April 10th and developed a papulovesicular rash on April 13th. He was transferred to the isolation building of the communicable disease hospital on the same day. He had generalized smallpox, complicated by pemphigus. He was vaccinated on April 9th and had a good take.

To recapitulate: Four individuals developed smallpox as a result of contact with an unrecognized case. Four other persons developed smallpox as a result of contact with one of the secondary cases and three others as a result of contact with another secondary case. Of the twelve individuals, nine had not been vaccinated before and three had been vaccinated in childhood, about forty years before. The diagnosis in all was confirmed by characteristic growth on chick embryo and a positive complement fixation reaction. The incubation periods varied from seven to sixteen days. There were two deaths, a mortality of 17 per cent.

STUDENT: I suppose there were many times during the outbreak when establishing or excluding the diagnosis of smallpox proved difficult. Could you tell us about that?

DR. GREENBERG: As Dr. Kneeland pointed out, the diagnosis of smallpox is not too difficult if the disease is suspected and if the clinical course and lesions are characteristic. At times during the recent outbreak, however, the differentiation between chickenpox and smallpox proved to be very difficult. Case IV, for instance, although never vaccinated, had no constitutional symptoms except fever for a few days and the rash was sparse and not pustular. It would undoubtedly have been diagnosed as chickenpox except that it occurred in the course of an outbreak of smallpox and confirmation of the diagnosis was received from the laboratory. On the other hand, during the course of the outbreak an adult Cuban was admitted with mild symptoms and a generalized vesiculopustular eruption. He had not been vaccinated since childhood. The rash was generalized and confluent and was profuse on the face, palms and soles, as well as on other parts of the body. The diagnosis shifted from chickenpox to smallpox and back as different physicians saw him. The diagnosis of chickenpox was finally agreed

to by all because of failure of laboratory confirmation of smallpox, because of the discrepancy between the profuseness of the rash and the mild constitutional symptoms and because on maturation of the pocks they were more like chickenpox than smallpox. Although it is true, as Leake points out, that the distribution of the rash is the most characteristic feature of smallpox, cases of chickenpox are occasionally seen which simulate the distribution of smallpox. The other features that differentiate the two diseases must then be taken into account in order to arrive at the proper diagnosis.

DR. A. RAYMOND DOCHEZ: Did this epidemiologic study throw any new light on the transmission of smallpox, especially in connection with air-borne transmission of the infectious agent?

DR. GREENBERG: The circumstances of the spread of smallpox within the communicable disease hospital suggest aerial transfer of droplet nuclei. Of the four secondary cases, two had been on the same floor in the observation building as the original patient, the third was on the third floor of the building and the fourth was on the sixth floor of the building. Since different personnel attended patients on the different floors and there was no interchange of linens or dishes, spread possibly occurred through aerial transfer of droplet nuclei.

DOCTOR: Is it because of the possibility of air-borne transmission that the Board of Health quarantines an entire building when a case of smallpox develops?

DR. GREENBERG: Yes, and the experience of this outbreak seems to vindicate the practice.

DR. ROSE: Dr. Greenberg, would you summarize the control measures undertaken to limit the spread of the disease.

DR. GREENBERG: Case II was admitted to the communicable disease hospital on March 27th, a tentative diagnosis of smallpox was made and on March 28th vaccination of all doctors, nurses, personnel and patients in the hospital was begun. Thereafter, all visitors to the hospital were vaccinated. As soon as a definite diagnosis of smallpox was made the following measures were taken:

Vaccination of Contacts. The building in the municipal hospital in which the dermatologic ward was located was quarantined and all patients and personnel vaccinated. Later the personnel and patients of the entire hospital were vaccinated. Also vaccinated were all personnel and patients who had visited the clinic on the day when Case III applied before going to the hospital. From the midtown hotel where the original patient resided lists of all guests registered there between March 1st and March 5th were obtained and all who were in the city were visited and vaccinated. Vaccination was also performed on all children who were exposed to the patients in the convalescent home and had returned to the city, as well as on the residents of the buildings in which Cases II and III lived.

Follow-up Visits. All contacts who had been discharged from the municipal and communicable disease hospitals and the convalescent home, all contacts who had lived in the midtown hotel and all residents of the buildings in which Cases II and III resided were visited daily by medical inspectors of the Department for a period of twenty-one days after the last exposure and examined for possible smallpox.

Notification. The United States Public Health Service was informed of the cases as they occurred and the names of contacts who lived outside of the city were forwarded for transmissal to the proper state health officers. The names of contacts who lived in New York State outside of the city were telephoned to the State Health Department, and lists of discharged patients from the convalescent home were received from the state authorities and followed-up. All hos-

pitals whose nurses affiliated with the communicable disease hospital were notified to vaccinate and to follow-up nurses who had left the hospital while the patients with smallpox were there.

Vaccination Campaign. The public was informed by the Commissioner of Health of the existence of smallpox in the city, using all means of communication—radio, press, lectures, etc. Vaccination was advised for those who had not been vaccinated recently. Physicians were offered vaccine free of charge for use in their practice, free clinics were opened in the central office and in all district health centers of the Department and arrangements were made with large employers of labor to have physicians of the Department visit their plants and offices and vaccinate all personnel.

The Department of Hospitals cooperated by opening free vaccination clinics in every municipal hospital and most of the voluntary hospitals opened clinics where vaccinations were performed free or for a small charge. Free clinics were later opened in all police precincts of the city, manned by physicians of the Department, and still later, vaccination was offered to school children of the city in their respective schools. In a period of three weeks more than 5,000,000 people were vaccinated.

DR. ROSE: Having considered the important clinical and epidemiologic features of smallpox, together with an intimate view of public health measures for its control, we shall now turn our attention to the etiologic agent, smallpox virus, and its relative, vaccinia virus. The discussion will be presented by Dr. Herald R. Cox, Director of the Section of Viral and Rickettsial Research, Lederle Laboratories.

DR. HERALD R. COX: The virus of smallpox is one of the larger of the agents classified as filterable viruses. It has a particle size averaging 0.2μ, according to indirect measurements made by filtration through graded collodion membranes and by sedimentation in the ultracentrifuge, as well as by the direct measurement of particles photographed with the aid of the electron microscope. The essential particles or elementary bodies of the virus are therefore just within the limits of visibility using the ordinary compound microscope, and advantage may be taken of this fact in the diagnosis of the disease. As Dr. Kneeland brought out, if scrapings of the cutaneous lesions in the acute vesicular or pustular stage from a suspected case of smallpox are smeared on slides and stained by certain methods, such as those of Giemsa, Castaneda or Goodpasture, the finding of elementary bodies by a person experienced in their identification lends weight to the diagnosis. It should be noted, however, that failure to observe elementary bodies by such a procedure by no means excludes the diagnosis of smallpox. Moreover, the elementary bodies of smallpox virus are indistinguishable morphologically from those of vaccinia virus.

The multiplication of smallpox or of vaccina virus in the tissues of the infected host is accompanied characteristically by the appearance of cellular inclusion bodies. Of these, the most typical is the Guarnieri body, which is a relatively large, round or oval structure, eosinophilic in its staining reaction and located in the cytoplasm. Acidophilic intranuclear inclusions are also seen in cells infected with smallpox virus, but not with vaccinia virus, a distinction of some importance from the standpoint of histopathologic diagnosis.

Two general methods are available for the specific diagnosis of smallpox in the laboratory, namely, the isolation and identification of the virus by inoculation o animals or chick embryos and the demonstration of specific antibodies to the virus in the blood of the patient. For isolating the virus from the cutaneous lesions the method

ordinarily employed is that first described by Paul. This consists of inoculating fluid or scrapings from the vesicular or pustular lesions onto the scarified cornea of a rabbit's eye. Two or three days after inoculation the cornea may appear slightly opaque and small vesicles or tiny shallow ulcers may be observed with the aid of a hand lens; painting the cornea with fluorescein is also useful in demonstrating their presence. The rabbit is sacrificed, the eye is enucleated and histologic sections of the cornea are prepared. Microscopic examination will reveal cellular proliferation and edema, together with areas of necrosis, and the pathognomonic Guarnieri bodies will be seen in the cytoplasm of some of the cells.

When the Paul test is positive the diagnosis is assured, but it must be pointed out that the test is negative in a considerable proportion of cases, especially when the disease is modified in character.

Another method for the specific demonstration of the virus in the cutaneous lesions without, however, actually isolating the agent consists in the performance of complement fixation or flocculation tests with antigens prepared from vesicles or pustules. Fluid from the vesicles or pustules is diluted with a little buffered saline, or crusts are ground up with the same diluent. These suspensions are then centrifuged and the supernatant fluids are used as the antigens. The antibody is serum from rabbits hyperimmunized by repeated injections of vaccinia virus. Flocculation tests are carried out by mixing dilutions of the antigen with dilutions of the antiserum and normal rabbit serum, incubating the mixtures and observing the appearance of a flocculent precipitate only in those tubes containing the antigen and the specific antibody. Using the same reagents, complement fixation tests may be performed in the usual manner, provided care is taken to dilute the antigen beyond the range of anticomplementary activity and to dilute the antiserum sufficiently so that prozone inhibition is eliminated. Of these tests the complement fixation test is the more sensitive and reliable and is the one usually employed.

The laboratory diagnosis of smallpox may also be effected by the demonstration of specific antibodies developed in the patient's blood during the course of his illness and convalescence. The method is that of complement fixation, using the patient's serum as antibody and an antigen prepared from vaccinia virus which has been propagated either on the chorioallantoic membrane of the chick embryo or in mice by intracerebral inoculation. As Dr. Greenberg indicated, this type of test was employed successfully by Dr. Smadel at the Army Medical School, Washington, D. C., to establish the diagnosis of smallpox in some of the patients observed during the recent outbreak in New York City. In the hands of competent persons who are experienced with complement fixation tests using viral antigens, the procedure is reliable and of great diagnostic value but it should not be undertaken by those who are unfamiliar with the pitfalls that may be encountered.

The precise relationship of the virus of vaccinia to that of smallpox is still an unsettled problem. The chief point at issue is whether vaccine virus is actually a modified form of smallpox virus to which the cow and other animals, including humans, are susceptible; or whether the virus of vaccinia is an entity separate from but closely related to the virus of smallpox. The weight of evidence inclines toward the former view but is insufficient to be conclusive.

The method of prophylactic vaccination against smallpox differs little today from that employed originally by Jenner since it simply involves the transfer of vaccine virus, in the form of infected calf lymph, to the human subject. The technic of preparation of vaccine virus for immunization is of some

interest. Calves of either sex, with negative immunologic tests for tuberculosis and brucellosis and preferably with non-pigmented skins, are employed for the propagation of the virus. The skin of the flanks and abdomen is carefully shaved and is washed repeatedly with sterile soap and water. Scarification of the skin is then done in parallel lines about 1 cm. apart, superficially so that no blood is drawn. Passage vaccinia virus is rubbed thoroughly into the scarified areas. The animals are kept in stalls with special sanitary arrangements so that surface contamination of the inoculated areas is reduced to a minimum. After five or six days confluent vesicles have formed along the lines of scarification. The skin is now carefully cleansed again with soap and water and the vesicles and their contents are removed by scraping with a special curette; little or no blood is drawn if this is done correctly. The mixture of vesicular fluid and tissue scrapings is known as vaccine pulp. Following collection of the vaccine pulp the animals are sacrificed. The pulp is used only if no evidences of tuberculosis or brucellosis are found on postmortem examination.

The fresh vaccine pulp is mixed with an equal part of sterile glycerine, quickly frozen and stored in the frozen state. Under these conditions bacteria occurring in the fresh pulp gradually die. At intervals after freezing, therefore, samples are removed and examined for residual bacteria. When the bacterial count has reached a level of about five organisms per milliliter and if no pathogenic clostridia are present, the vaccine is tested for potency of the virus. This may be done either by inoculating non-immune human subjects or by titration into the skin of rabbits; in practice the latter method is usually employed.

It is of considerable importance that the vaccine virus tends to lose its potency if passaged serially in calves alone, but that the potency may be maintained if interval transfers are made either in man or rabbit. In general, it is customary to transfer the virus intracutaneously to rabbits after every second or third passage in the calf and then to return the virus to the bovine host. In this manner the potency of the virus can be kept at a high level, apparently for an indefinite time.

When the glycerinized vaccine has been found to be satisfactory, as regards both bacterial contamination and virus potency, it is distributed for use. If kept at low temperatures, it will retain its potency for several months but if the environmental temperature is raised much above freezing the virus deteriorates within a week or two.

A number of attempts have been made to introduce a vaccine prepared from vaccinia virus, cultivated either in tissue cultures or in the developing chick embryo. The virus can be grown easily by either of these methods, which have the advantage that there is complete freedom from bacterial contamination. This type of vaccine has not found favor up to the present time, however, since there is some question that the virus may be altered antigenically under these conditions and thereby lose its ability to immunize effectively the susceptible human subject against smallpox. Nevertheless, this is not a closed issue and the possible development of an effective vaccine using vaccinia virus grown outside the animal host is one of the many important problems that remain to be solved in connection with smallpox.

DR. ROSE: Dr. Greenberg referred to the isolation of smallpox virus in chick embryos from patients in the New York City outbreak. Can you tell us something about this procedure as a method of diagnosis?

DR. COX: Smallpox virus may be readily cultivated in the developing chick embryo and many isolations of the virus directly from man have been made by this method. Material from pustules is inoculated into

the chorioallantoic membrane where growth of the virus is indicated by the appearance of pock-like lesions. Once the virus has been established in the chick embryo it may be maintained indefinitely by serial passage. The identity of the virus may be suspected by the character of the lesions produced on the chorioallantoic membrane and is confirmed by neutralization tests with specific antiserum.

The use of chick embryos for primary isolation of the virus is an excellent method for the specific laboratory identification of smallpox, although it must be said that a negative result does not exclude the diagnosis.

DR. ROSE: We come now to the important matter of vaccination. Dr. Kneeland, would you begin with a brief outline of the technic of vaccination.

DR. KNEELAND: First, it is of paramount importance to preserve the vaccine virus at icebox temperature and not to expose it to room temperature for any considerable time before use. The vaccine deteriorates rapidly on warming and this may account for many failures. The area to be vaccinated should be cleansed with soap and water and allowed to dry thoroughly. It is probably best not to use any other antiseptic, such as alcohol, for traces of it can inactivate the virus. At present the multiple pressure method is generally recommended and seems to have certain advantages. Lastly, it has been shown that the likelihood of secondary infection is diminished if the vaccination site is left uncovered.

A very good discussion of this topic will be found in an article by Leake* which is available in reprint form.

STUDENT: Why is so much emphasis put on not applying a tight covering to the site of vaccination?

DR. GREENBERG: Experience has shown that the hazard of infection is greater if a tight covering is applied. Moreover, a dressing is likely to adhere to the secretion and thus interfere with the formation of a firm crust.

DR. ROSE: A tight covering favors the growth of anerobic bacteria which may be present on the skin at the time of vaccination. The tetanus bacillus is especially important in this respect and at one time tetanus was not an uncommon complication of vaccination. This has been rare in recent years.

DR. GREENBERG: Not one case of tetanus turned up following the recent mass vaccination.

DR. KNEELAND: Something should be said about the clinical features of vaccination, although this may seem superfluous to an audience, the majority of whom have been vaccinated recently. Those of you who have had a "primary take" must be thoroughly familiar with the sequence of events (Fig. 3)—how for three days or so nothing happened, then a papule appeared which turned into a vesicle at the end of a week and became pustular at the ninth or tenth day. At this time you may have noticed local and constitutional symptoms, including chills and fever. By the fourteenth day you were better and a firm crust covered the lesion. This train of events, as I said, characterizes the "primary take"; it occurs regularly in first vaccinations and in revaccinations when the individual's immunity has become low. When you have had this kind of response you may be pretty certain you are immune.

You may make the same assumption if you have had an "accelerated" or "vaccinoid" type of reaction. Here the papule appears in a day or two, becomes vesicular and then pustular a couple of days later, to subside by the end of a week leaving a small scab. This indicates a positive reaction in a person whose immunity is fairly high, but I wish to caution you against placing

* LEAKE, J. P. Questions and Answers on Smallpox and Vaccination. *Public Health Rep.*, 60: 221, 1927.

too much confidence in the so-called "immediate" or "immune" response. By these terms is meant a papule which develops almost at once and subsides in a few days without going through the stages of vesiculation and pustulation. Quite true, this is the sort of reaction one expects in an individual whose immunity is of a high order but it also may mean no reaction at all, i.e., it may be the result of faulty technic of vaccination or improper handling of the virus. Emphasis has been placed on this by writers for the Army Medical Bulletin, who believe that the occurrence of smallpox in our "immune" troops may have been due in part to misinterpretation of the so-called accelerated or immune reaction. Lastly, I must urge you personally to examine all the people you vaccinate at appropriate intervals in order to evaluate the response.

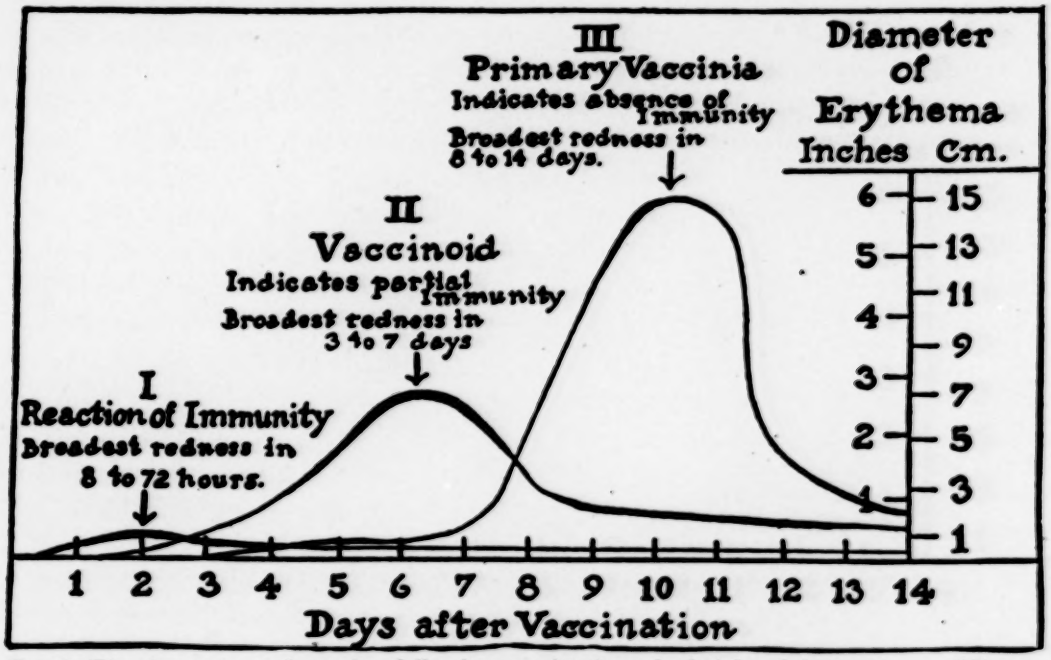


FIG. 3. The three types of reaction following vaccination; the height of the curves on different days indicates the diameter of the erythema. (From LEAKE, J. P. *Public Health Rep.*, 60: 221, 1927.)

DOCTOR: How do you deal with "immune reactions"?

DR. KNEELAND: That is a difficult question to answer. If you are vaccinating considerable numbers of people and getting a respectable number of primary takes, you can be relatively confident of the technic and potency of the vaccine virus. Then the finding of a few immune reactions in individuals with histories of fairly recent vaccinations should not be disturbing. On the other hand, if many immune reactions are obtained, particularly in patients who have not been vaccinated in years, this is cause for suspicion of either the technic or the lymph and calls for revaccination. If I were dealing with troops, let us say, who were about to enter an area where smallpox was endemic, I should be inclined to revaccinate at least once all those who showed an immune response. Let me emphasize again how important it is to examine repeatedly all individuals after vaccination who are at all likely to be exposed to the disease.

DR. HOWARD BRUENN: What are the contraindications to vaccination?

DR. GREENBERG: We advise against vaccination in the first trimester of preg-

nancy; ill effects in the offspring are not known to occur but in view of what has been discovered concerning the effects of German measles virus it is considered prudent to regard early pregnancy as a contraindication. Patients with generalized dermatoses and those with acute infectious diseases also should not be vaccinated.

DR. FREDERICK K. HEATH: A problem that arose during the outbreak concerned surgical procedures following vaccination. How long an interval after vaccination should elapse before operative procedures may be performed safely?

DR. GREENBERG: Vaccinia virus may be present in the blood for several weeks after vaccination. It would seem wise, therefore, to postpone elective operations for several weeks.

STUDENT: How often should vaccination be performed to furnish adequate immunity?

DR. ROSE: Vaccination should be repeated every five to ten years under ordinary circumstances, with the understanding that individuals vary widely in the rate at which immunity is lost. If, however, a person is to reside in any area where smallpox is endemic and severe, as in the Far East, then revaccination at yearly intervals is recommended.

DOCTOR: What about "false positive" serologic tests for syphilis following smallpox vaccination?

DR. ROSE: In 1940, Barnard observed that smallpox vaccination may be followed by the transient appearance of positive complement fixation and flocculation tests for syphilis in persons who are non-luetic. Since then a number of studies have amply confirmed this fact and have established the overall incidence at approximately 15 per cent. Rein and Ellsberg* have shown that positive tests develop most frequently following primary vaccinia, less frequently after a "vaccinoid" reaction and least often after the so-called "immune" response to vaccination.

Positive serologic tests for syphilis appear one to two weeks after vaccination and usually disappear quickly within another two or three weeks but in some patients they may remain positive for several months. Fortunately, the reactions are mostly of low titer and will rarely be confused with the high titered reactions ordinarily encountered in patients with untreated syphilis, but this criterion alone cannot be relied upon to effect a distinction between the presence or absence of luetic infection. Whenever syphilis is suspected from the evidence of positive serologic tests the question of recent vaccination should be routinely included in the history.

DR. GREENBERG: Dr. Rosenthal has followed some of the persons vaccinated during the recent outbreak and he informs me that about 10 per cent of his series gave serologic reactions for syphilis which were positive in some degree.

DR. HEATH: One aspect of great practical importance has not yet been touched upon, the nature and incidence of postvaccinal encephalitis.

DR. ROSE: The nature of postvaccinal encephalitis or, more properly, encephalomyelitis, is not entirely clear. The disease is an acute meningo-encephalitis which ordinarily appears from seven to fourteen days following vaccination. It is a rare complication and has been found to occur, on the average, about once in every 100,000 persons vaccinated. However, in some series the incidence has been reported as high as 1 in 20,000.* Apparently the disease is observed most frequently in children following primary vaccination; it is much less common in both children and adults following revaccination.

The onset is usually abrupt and the

* REIN, C. R. and ELLSBERG, E. S. *Am. J. Syph.*, 29: 303, 1945.

* MARSDEN, J. P. *Bull. Hyg.*, 21: 555, 1946.

course may be characterized by headache, fever, vomiting, paralyses, coma and convulsions. The signs are commonly those of a diffuse cerebral involvement, although in some patients the predominant symptoms are those of cord involvement, including the anterior horns.

The pathologic changes are essentially those of an acute, widespread demyelination and they are similar to the lesions seen in patients with encephalomyelitis following measles, chickenpox or antirabic vaccination. The same type of encephalomyelitis also occurs in patients suffering from smallpox, regardless of antecedent vaccination, and the incidence there is about 1 in 2,000.

The mortality rate from postvaccinal encephalomyelitis is high and ranges from 30 to 60 per cent.

The etiology is still not definitely known. Attempts to isolate vaccinia virus and other neurotropic viruses from the central nervous tissue of fatal cases have been almost uniformly unsuccessful and it would therefore appear that the disease is not caused by the direct action of vaccinia virus or the activation of other latent viruses. However, another possibility is that the syndrome is caused by some form of sensitization or allergic response. The incubation period with adequate time for antibody formation, together with the failure to recover vaccinia virus, suggests this possibility. Moreover, in those cases that occur following revaccination the incubation period is shortened and the onset is accelerated, which may indicate an anamnestic type of immune response. Finally, it may be noted that an acute disseminated encephalomyelitis may be produced experimentally in monkeys by the injection of brain tissue combined with certain adjuvants. This experimental disease closely resembles postvaccinal encephalomyelitis both clinically and pathologically and is clearly the result of an immunologic phenomenon.

DR. HEATH: There has been much loose talk about postvaccinal encephalomyelitis following the recent mass vaccination in New York. Can you give us the facts, Dr. Greenberg?

DR. GREENBERG: We have been following a number of cases of individuals who have had symptoms resembling encephalomyelitis following their vaccination. We have also investigated deaths of all such individuals.

Fortunately, we have been able to obtain autopsies in all of the cases. At the present time we have records of five deaths in which encephalomyelitis was suspected of being the cause of death. One of these patients lived out of town. The brain was examined by two competent pathologists, neither of whom found any evidence of inflammatory lesions. A similar case occurred in New York City and the brain was examined by Dr. Rivers of the Rockefeller Institute. No inflammatory lesion was found. Two of the cases were examined by the Medical Examiner's Office and were found to have had tuberculous meningitis. The fifth death was also a medical examiner's case. Dr. Gonzales informs me that there were sufficient lesions of the circulatory system to account for the death. There was nothing found on gross pathologic examination of the brain but the sections have not yet been run.

Thus, up to the present, we have not had a single death that could be ascribed to encephalitis following vaccination.

SUMMARY

DR. HEATH: The recent outbreak of smallpox in New York City not only emphasized how casual is the acquaintance most physicians have with the disease but also clearly showed the many defects in our knowledge concerning it. On the other hand, the happy outcome of events furnished striking testimony to the efficiency of epidemiologic and public health measures when properly applied and serves as a

tribute to the New York City Board of Health.

The usual incubation period of variola is twelve days, although variations from five to twenty-one days are not unknown. The period of invasion follows, lasting three to four days, characterized by chills, fever, prostration, muscular aches, headache, nausea and vomiting. Rather suddenly, the macular eruption then appears on the face and distal upper extremities, accompanied by a decrease in the symptoms and fever. The rash progressively becomes papular, vesicular and pustular, terminating by crusting and desquamation in about two to four weeks. An ulcerating enanthem may accompany the exanthem. In fatal cases the ordinarily transient secondary fever appearing with pustulation remains to the end. In general, the mortality is higher the more marked the fever and the eruption, death resulting from overwhelming viral infection, sepsis or pneumonia. Smallpox modified by immunity resulting from vaccination may pursue an atypical abbreviated course and confusion with chickenpox may be unavoidable. During the invasive period of the disease, when a morbilliform or scarlatiniform rash may be present, measles or scarlet fever may be suspected; if no rash is present the disease may be indistinguishable from a variety of febrile conditions.

A variety of diagnostic procedures, all requiring expert technic, are available to aid in laboratory diagnosis. Material from the vesicles or pustules may be examined either by direct smear and search for elementary bodies or more specifically by growing the material on the rabbit cornea (Paul test) or chick embryo. Finally, complement fixation or flocculation technics may be used to demonstrate specific antigens in the lesions by titration with high titer rabbit antiserum, or the development of antibodies in the blood of the patient may be determined by the complement fixation method using known vaccinia virus as antigen.

In connection with vaccination, emphasis is placed on using potent vaccine since potency lasts only a few months after preparation and decreases rapidly when the vaccine is stored above freezing temperatures. The dangers of bandaging are pointed out but no mention is made of the disability following leg vaccination, frequent and severe enough to disqualify this as a procedure of choice. The significance and characteristics of the primary and accelerated takes are noted; an immune type of reaction, unless it occurs in a recently vaccinated individual, may be due to poor vaccine or faulty technic and calls for revaccination. At this time, pregnancy in its first trimester, acute infectious disease and generalized skin disease are regarded as the only contraindications to vaccination. Elective surgery should be postponed following vaccination although urgent procedures have been performed without ill effect. The duration of immunity resulting from a successful vaccination varies with the individual. Vaccination should be repeated every five to ten years ordinarily and in endemic areas revaccination should be carried out at least annually.

An interesting complication of vaccination is a diffuse meningo-encephalitis bearing a mortality of from 30 to 60 per cent and possibly representing an allergic response in the central nervous system. As yet there is no evidence, except temporal, to suggest that this is a viral infection.

An account of the New York City outbreak discloses the hazards of wrong diagnosis and the rapid spread of the disease among non-immune subjects even though not in direct contact with the disease. The tremendous task of limiting such a potential epidemic and the measures used are detailed in the text. No more effective argument for compulsory vaccination can be advanced.

Clinico-pathologic Conference

Hypertension with Papilledema*

STENOGRAPHIC reports, edited by Robert J. Glaser, M.D., of weekly clinico-pathologic conferences held in the Barnes Hospital are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient, E. S., was a thirty-nine year old machinist who entered the Barnes Hospital on November 28, 1946 complaining of headache, vomiting and blurring of vision. The family history was non-contributory. The patient had enjoyed generally good health. System review revealed that for several years his hearing had been gradually failing; one year before entry the patient had a penile lesion for which he received penicillin and arsenic treatment over a period of six months with apparent recovery. His diet had been adequate and his alcoholic intake was moderate.

In July, 1946, the patient developed pain and swelling of the knees, hands, wrists and ankles lasting about one month. The joints were said to have been painful and somewhat swollen but not red. There had been no evidence of preceding infection. Shortly after the onset of the arthritis the patient had ten or twelve episodes during which he suddenly lost consciousness. The attacks occurred while he was ambulatory as well as recumbent and lasted only several minutes. His arms and legs became stiff before an attack but as far as was known he had had no convulsions. After several weeks the attacks ceased and thereafter did not recur. The patient was advised by his physician to go to a spa and while there, another physician told him that he had tuberculosis, although at no time had he had any pulmonary symptoms. He was advised to go to Arizona which he did; during his stay he had several episodes of cramping abdominal pain. He had no other gastrointestinal symptoms and he remembered no further details about this phase of his illness. Three weeks before entry to the hospital, he returned to his home in Illinois and soon thereafter began to have headaches of increasing severity, localized in the orbital and the temporal areas. The headaches were described as pulsating in character and they soon became constant. Two weeks prior to admission the patient began to vomit about three times a day although he did not complain of nausea. Vomiting persisted and he was able to take very little nourishment. Three days prior to entry his vision became blurred. The headaches and vomiting increased and he was referred to this hospital.

At the time of entry the physical examination revealed the temperature to be 37.3°C., pulse 85, respirations 16 and blood pressure 230/140. The patient appeared chronically ill and older than his stated age; he lay flat in bed holding his head and at times cried with pain. He answered questions only with great difficulty. The skin was sallow and dry. Several large, rubbery, discrete, nontender lymph nodes were noted in the inguinal regions and a few shotty, axillary nodes were also palpable. Exophthalmos was noted. The pupils were round, regular and equal and reacted to light and accommodation. Examination of the fundi

* From the Departments of Internal Medicine and Pathology, Washington University School of Medicine and the Barnes Hospital, St. Louis, Mo.

revealed bilateral papilledema, many hemorrhages and exudates and marked arteriolar narrowing. The eardrums were thickened and somewhat retracted and hearing was impaired bilaterally. The teeth were carious. Examination of the lungs revealed them to be clear to percussion and auscultation. The heart was not enlarged, the rhythm was regular and the sounds were of good quality. The second aortic sound was accentuated. No murmurs were heard. The peripheral arteries were thickened and the temporal arteries were tortuous. Examination of the abdomen revealed no palpable organs or masses. A scar was noted on the glans penis. On rectal examination no abnormal masses were felt. Neurologic examination showed a peripheral right seventh nerve weakness; no other significant neurologic findings were described.

The laboratory studies were as follows: Blood count: red cells, 4,200,000; hemoglobin, 10.6 Gm.; white cells, 17,500; differential count: eosinophiles, 2 per cent; stab forms, 2 per cent; segmented forms, 62 per cent; lymphocytes, 32 per cent and monocytes, 2 per cent. Urinalysis: specific gravity, 1.015; albumin, 4+; sediment, 2 to 3 hyaline casts and 8 to 12 red cells per high power field. Blood Kahn test: negative. Blood chemistry: non-protein nitrogen, 30 mg. per cent; total proteins, 4.6 Gm. per cent; albumin, 2.8 Gm. per cent; globulin, 1.8 Gm. per cent; calcium, 10.4 mg. per cent; phosphorus, 3.8 mg. per cent; chlorides, 89 meq. per liter and carbon dioxide combining power, 51.5 volumes per cent. Venous pressure: 100 mm. NaCl. Circulation time (decholin): 17 seconds. Electrocardiogram: indeterminate. Roentgenograms: "The bones of the skull appear thicker than usual. The sella turcica is within normal limits. No areas of destruction are visualized. The cardiac silhouette is within normal limits. The aorta is slightly lengthened. Minute deposits of calcification and a minimal amount of fibrosis are seen in the apices of both lungs, but there is no evidence of active pulmonary disease. An open film of the urinary tract and intravenous pyelography are unsatisfactory."

Shortly after entrance to the hospital the patient was seen by a neurologic consultant who confirmed the findings described in the physical examination. He also noted a downward drift of the right arm on extension, indicating left cerebral localization. At his suggestion a lumbar puncture was performed. The initial pressure was 440 mm. of water and the final pressure 180 mm. of water. Ten cc. of clear fluid were removed. There were 3 cells. The protein was 123 mg. per cent and the Ayala index was 4.1. The patient exhibited no untoward reaction to the procedure.

The patient was somewhat obtunded and his condition was unchanged until the fifth hospital day when he had a generalized clonic convulsion, lasting several minutes. Repeat laboratory studies at that time showed the non-protein nitrogen to be 31 mg. per cent; the carbon dioxide combining power, 61 volumes per cent and the serum chlorides, 94 meq. per liter. Urinalysis again showed albuminuria and the sediment contained occasional hyaline casts and a few red cells per high power field. The patient was given large amounts of fluid daily and passed urine of low specific gravity. One week following entry he was noted to have developed bilateral hydrothorax and sacral edema. At that time his red blood count was 3,570,000, the white count, 14,000. The differential count showed a slight shift to the left.

On the tenth hospital day the patient had another generalized convulsion lasting several minutes. For twenty-four hours previously he had complained of increasing headaches; nausea and vomiting, which had been persistent throughout his hospital stay, had increased. For the convulsion he was

given 20 cc. of 25 per cent magnesium sulfate intravenously. His condition became progressively worse and he died on December 8, 1946, the eleventh hospital day. During the period of hospitalization his temperature at no time had risen above 37.5°C. His pulse had varied between 110 and 130 and his blood pressure averaged 210/120.

CLINICAL DISCUSSION

DR. HARRY L. ALEXANDER: Whether or not it will be possible to fit all of the symptoms with which this patient was afflicted into a single clinical picture is problematical. Among other things he complained of arthritis, convulsions, abdominal pain, headaches and blurred vision. On physical examination the most conspicuous findings were those related to the vascular system, particularly the diastolic hypertension. Dr. Schroeder, would you care to suggest what type of hypertension this may have represented?

DR. HENRY A. SCHROEDER: The problem here is difficult, for there is no history of hypertension prior to the patient's admission to the hospital, therefore, it is not clear whether this was an acute or chronic phenomenon. At the time of entry he exhibited the syndrome called malignant hypertension which is characterized by a high diastolic blood pressure, cardiac enlargement, retinopathy, elevated non-protein nitrogen and abnormalities in the urine, such as albuminuria and hematuria. The fact that the patient's heart was not enlarged indicates that the hypertension may have been relatively acute in onset.

DR. ALEXANDER: It was noted in the physical findings that the patient had thickening of the peripheral arteries and tortuosity of the temporal vessels. How long must hypertension be present in order to produce such changes?

DR. SCHROEDER: It takes a relatively long time. When peripheral arteries are described as being thickened, it is not always clear as to whether the examiner means a "rubbery" thickening, such as is seen in hypertrophy of the muscular coat in long-standing elevation of the diastolic pressure, or whether the thickening is of the "egg shell" variety which is common in arteriosclerosis. The tortuosity described in the temporal vessels could be either, but is more likely arteriosclerotic.

DR. ALEXANDER: On the *x*-ray film of the chest the aorta appeared somewhat lengthened. Do you believe that this finding is evidence of hypertension or more than several months' duration?

DR. SCHROEDER: I do not think that one can say. Aortic lengthening may be due to hypertension or it may be due to arteriosclerosis. All of the findings described, with the exception of those in the fundi, could be explained by arteriosclerosis alone.

DR. ALEXANDER: Dr. Moore, do you know how long it would take for sufficient hyperplasia of the peripheral vessels to give rise to thickening or lengthening?

DR. ROBERT A. MOORE: I know of no studies that offer an answer to that question. I think it can be said, however, that if the disease process existed fully developed for a year, there would certainly be anatomic changes. Whether over a much shorter period similar changes could arise, I do not know.

DR. ALEXANDER: Dr. Massie, the cardiac examination was rather unimpressive despite the marked hypertension. How long do you believe it would take for hypertension of the degree recorded here to cause changes in cardiac size?

DR. EDWARD MASSIE: There is considerable individual variation in cardiac response to hypertension and I do not believe that a definite answer can be given to your question.

DR. SCHROEDER: I believe that it is possi-

ble for hypertrophy to be present without dilatation; in such an instance the heart size might appear normal on *x*-ray.

DR. ALEXANDER: I think that we can consider that this man had malignant nephrosclerosis. Dr. Levy, do you believe that he may also have had a brain tumor?

DR. IRWIN LEVY: Possibly.

DR. ALEXANDER: Some years ago, before malignant hypertension was established as a clinical entity, hypertensive patients with the presenting complaints of severe headache and papilledema were often erroneously thought to have a brain tumor and craniotomy was not infrequently performed. Such confusion can be understood when one considers that the eye ground changes may be somewhat similar and there may indeed be focal neurologic signs. Dr. Schroeder, this patient's spinal fluid pressure was elevated. In malignant nephrosclerosis is a high spinal fluid pressure common and if so, what is the mechanism?

DR. SCHROEDER? It is usually thought to be due to cerebral edema.

DR. ALEXANDER: Is the protein of 123 mg. per cent compatible with cerebral edema?

DR. LEVY: I think that it is more in keeping with brain tumor than with malignant hypertension and cerebral edema *per se*.

DR. ALEXANDER: The headaches, retinal changes and increased spinal fluid pressure are all consistent with the diagnosis of brain tumor, are they not?

DR. LEVY: Yes.

DR. ALEXANDER: Against the diagnosis of brain tumor is the marked degree of renal involvement evidenced by albuminuria and hematuria. Unless the hypertension had been present for some time it would be difficult to explain the renal findings. On the other hand, the high spinal fluid protein is not in keeping with malignant hypertension. Dr. Wood, do you care to comment?

DR. W. BARRY WOOD, JR.: I do not believe that the renal changes can be explained on the basis of a brain tumor and I think another possibility, other than nephrosclerosis, should be considered. This patient may have had periarteritis nodosa which would have accounted for his initial arthritis, for the attacks of abdominal cramping and for the terminal picture of advanced renal disease. Furthermore, arterial lesions in the central nervous system could have given rise to the elevated spinal fluid protein.

DR. ALEXANDER: I agree that an excellent argument can be made in favor of periarteritis nodosa.

DR. WOOD: Dr. Carl V. Moore saw this patient on the ward. His first diagnosis was malignant nephrosclerosis but he suggested periarteritis nodosa as an alternate possibility.

DR. MASSIE: Is a six-months' history rather short for periarteritis nodosa?

DR. ALEXANDER: I do not think so. I am somewhat disturbed, however, by the absence of fever.

DR. WOOD: In most of the patients with periarteritis nodosa whom I have seen there has been fever. We should mention, however, that this patient did have a leukocytosis, which favors periarteritis nodosa over either malignant nephrosclerosis or brain tumor.

DR. ALEXANDER: Yes, a leukocytosis is very characteristic. Had there been fever the clinical picture would have been perfect for periarteritis nodosa. Yet, this disease has many variants, therefore, the absence of fever does not invalidate the diagnosis.

DR. WOOD: It is, of course, entirely possible that prior to his entry to the hospital, with some of his other episodes, the patient may have had an associated rise in temperature.

DR. ALEXANDER: Dr. Schroeder, would you comment further on the renal lesion of malignant nephrosclerosis?

DR. SCHROEDER: If the patient had malignant nephrosclerosis, one would expect to find arteriolitis involving the renal arterioles.

DR. ALEXANDER: Are not those lesions necrotizing?

DR. SCHROEDER: Yes, the necrotizing arteriolitis distinguishes the lesion of malignant nephrosclerosis.

DR. ALEXANDER: I believe that the lesions of periarteritis nodosa likewise are characterized by necrotizing panarteritis. I should like to ask Dr. Robert Moore whether in periarteritis nodosa the small arteries are involved?

DR. R. A. MOORE: In polyarteritis the disease process involves the medium-sized and large arteries rather than the arterioles. In my opinion the lesion in both lupus erythematosus and polyarteritis differs fundamentally from the lesion of malignant nephrosclerosis. In the first two, the process is predominantly inflammatory, whereas in the latter necrosis is characteristic. There is practically no reaction of an inflammatory character seen in malignant nephrosclerosis.

DR. SHERWOOD MOORE: Would you comment on the exophthalmos described in the physical examination.

DR. ALEXANDER: I believe that in extreme hypertension, exophthalmos has been described.

DR. PALMER H. FUTCHER: Dr. Warfield T. Longcope used to point out patients with chronic nephritis and hypertension who exhibited exophthalmos.

DR. WOOD: In this connection, mention should be made of the so-called "uremic stare," described some years ago by Hanes. Patients with uremia may indeed have extreme exophthalmos, suggesting a diagnosis of exophthalmic goiter. The patient under discussion today, however, did not have significant nitrogen retention.

DR. ALEXANDER: This patient during his hospital course developed bilateral pleural effusion and sacral edema. Dr. Massie, do you believe that these features were cardiac in origin?

DR. MASSIE: The physiologic tests of cardiac function were all within normal limits but I see no other explanation for the edema; I do not believe that the serum albumin was low enough to cause edema.

DR. ALEXANDER: Dr. Futcher, how do you explain the low serum chloride?

DR. FUTCHER: Two possible reasons for hypochloremia come to mind. In the first place, the patient vomited considerably and in the second place, he may have had so-called "salt-losing nephritis."

DR. ALEXANDER: Do you wish to comment on the edema?

DR. FUTCHER: The serum albumin was somewhat below normal values and it is conceivable that that, plus a minimal degree of heart failure, may have been responsible. It is also true that patients with arterial diseases develop pleural effusion apparently as a result of inflammatory changes. The patient did not complain, however, of pleurisy.

DR. SAMUEL C. BUKANTZ: Dr. Alexander, would you care to comment on the possible relationship between the antibiotic therapy and the development of possible periarteritis nodosa six months later. The patient received penicillin shortly before his first symptoms appeared.

DR. ALEXANDER: I think your suggestion is an interesting one but as yet, no one has described periarteritis resulting from hypersensitivity to penicillin. The patient was also given arsenic but I doubt whether that compound could have initiated the process.

DR. FUTCHER: Returning to the possibility of a brain tumor, I wonder if Dr. Levy would tell us where this tumor may have been located.

DR. LEVY: I could not localize it any more than to say that it was in the left hemisphere.

DR. KEITH S. WILSON: May the patient have had a gumma of the brain?

DR. VIRGIL C. SCOTT: I believe that the time interval for the development of a gumma is too short.

DR. ALEXANDER: Could the lesion have been a tuberculoma?

DR. LEVY: I think that is possible. If I had to pick out a single neurologic lesion however, on the basis of a short history with seizures, I would suggest glioblastoma multiforme.

DR. ALEXANDER: In summary, the diagnoses of malignant nephrosclerosis, periarteritis nodosa and brain tumor have been suggested as an explanation of this patient's illness. The consensus of the opinion of the staff seems to favor a diagnosis of periarteritis nodosa. Are there other questions?

STUDENT: Would Dr. Massie comment on the tachycardia?

DR. MASSIE: I believe the tachycardia was merely a reflection of the terminal illness.

Clinical Diagnosis: Periarteritis nodosa.

PATHOLOGIC DISCUSSION

DR. RICHARD E. JOHNSON: At the time of autopsy external inspection of the body revealed no abnormalities. The right thorax contained 700 cc. of clear, straw-colored fluid and 100 cc. of similar fluid were present on the left side. The heart weighed 430 Gm. In the lungs there were calcified fibrous scars at both apices and a calcified nodule in the right lower lobe. Four hundred cc. of fluid were present in the peritoneal cavity. The liver showed several small, depressed, purple areas immediately beneath the capsule. On cut surface these were red and soft. The cystic artery was readily palpable throughout its course over the gallbladder. The hepatic, splenic and mesenteric arteries were not remarkable. The most interesting findings were in the kidneys. They were slightly reduced in size, weighing 140 and 130 Gm., respectively. The external surface

FIG. 1. Photograph of kidney showing irregular nodularity.

showed marked irregular nodularity with large islands of elevated yellow tissue cut off by depressed, grayish-red, firm foci. On cut surface the depressed red areas extended throughout the width of the cortex but not into the medullary zone. The interlobar and arcuate arteries were unusually thickened. Examination of the bladder showed ecchymoses and petechiae in the mucosa. The brain showed flattening of the gyri with partial obliteration of the sulci. Multiple coronal sections revealed no additional anatomic changes.

DR. R. A. MOORE: The gross examination of the kidneys (Fig. 1) showed characteristic changes in the surface with large nodules, irregular in size and shape, yellow in color, retaining the structure of the renal cortex. Between the nodules there were depressed areas, irregular in outline, red or reddish-gray in color, obviously composed of fibrous tissue. Throughout the renal substance, particularly in the elevated areas, petechiae in varying sizes up to 1 mm. in diameter were seen. The large flat U-shaped scars suggested chronic pyelonephritis. The only point against that diagnosis was the fact that the changes in the renal pelvis were not as marked as those in the renal parenchyma. The character of the preserved tissue indicated that the patient had some degree of arteriolar nephrosclerosis which had gone

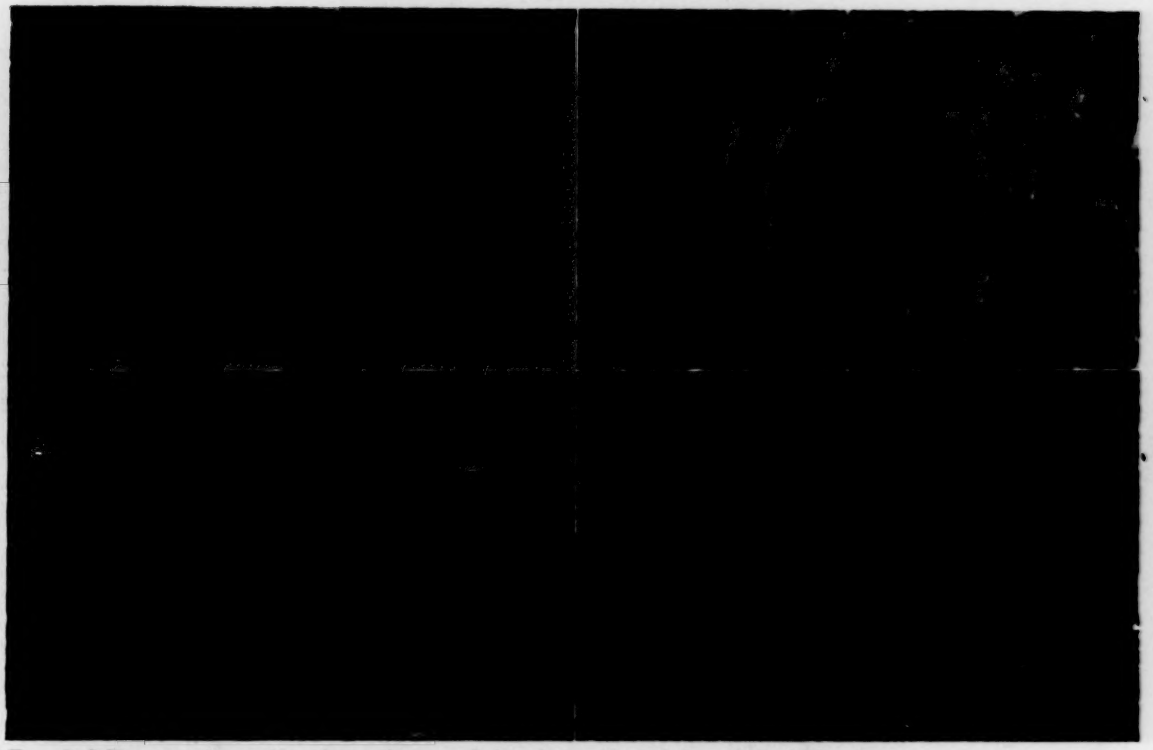


FIG. 2. Microscopic section through one of the elevated nodules of the kidney.
FIG. 3. Section of the kidney showing a glomerulus. Note necrosis of the entering arteriole.
FIG. 4. Another section through the kidney showing a glomerular adhesion. Note the epithelium of the convoluted tubule opposite the entering arteriole. It represents a portion of the juxta-glomerular apparatus.
FIG. 5. Section of the kidney showing the changes of infarction of a glomerulus.

on to the malignant phase. Accordingly, on the basis of the gross observations, diagnoses of chronic pyelonephritis and arteriolar nephrosclerosis with petechiae were made.

Let us now turn to the microscopic findings. Figure 2 shows a characteristic section through one of the elevated nodules; the renal substance is moderately well preserved. There is an increase in connective tissue, great thickening of the arteries and arterioles and necrosis in a part or all of the walls of the thickened arterioles with very slight cellular infiltration. These lesions are characteristic of arteriolar disease but they are not uniform. When individual vessels were reconstructed by step sections it was found that there were plaque-like lesions either in the media or intima.

In Figure 3 there is a glomerulus which shows necrosis of the entering arteriole. There are thrombi in the lumen of the primary capillary branches of that vessel. There are also degenerative changes in the renal tubules and very slight increase in connective tissue with edema of the interstitial substance of the kidney. In another glomerulus (Fig. 4) a glomerular adhesion may be seen and there is a change in the cellular type of epithelium lining Bowman's capsule. It is well to point out that in the distal convoluted tubule the epithelium directly opposite the entering arteriole is very tall and represents a part of the juxta-glomerular apparatus, about which there has been much discussion in the past ten years. In other glomeruli dilatation of the capillaries with thickening of the basement membrane was seen. Some of the glomeruli show an increase in the number of nuclei and an occasional glomerulus has undergone

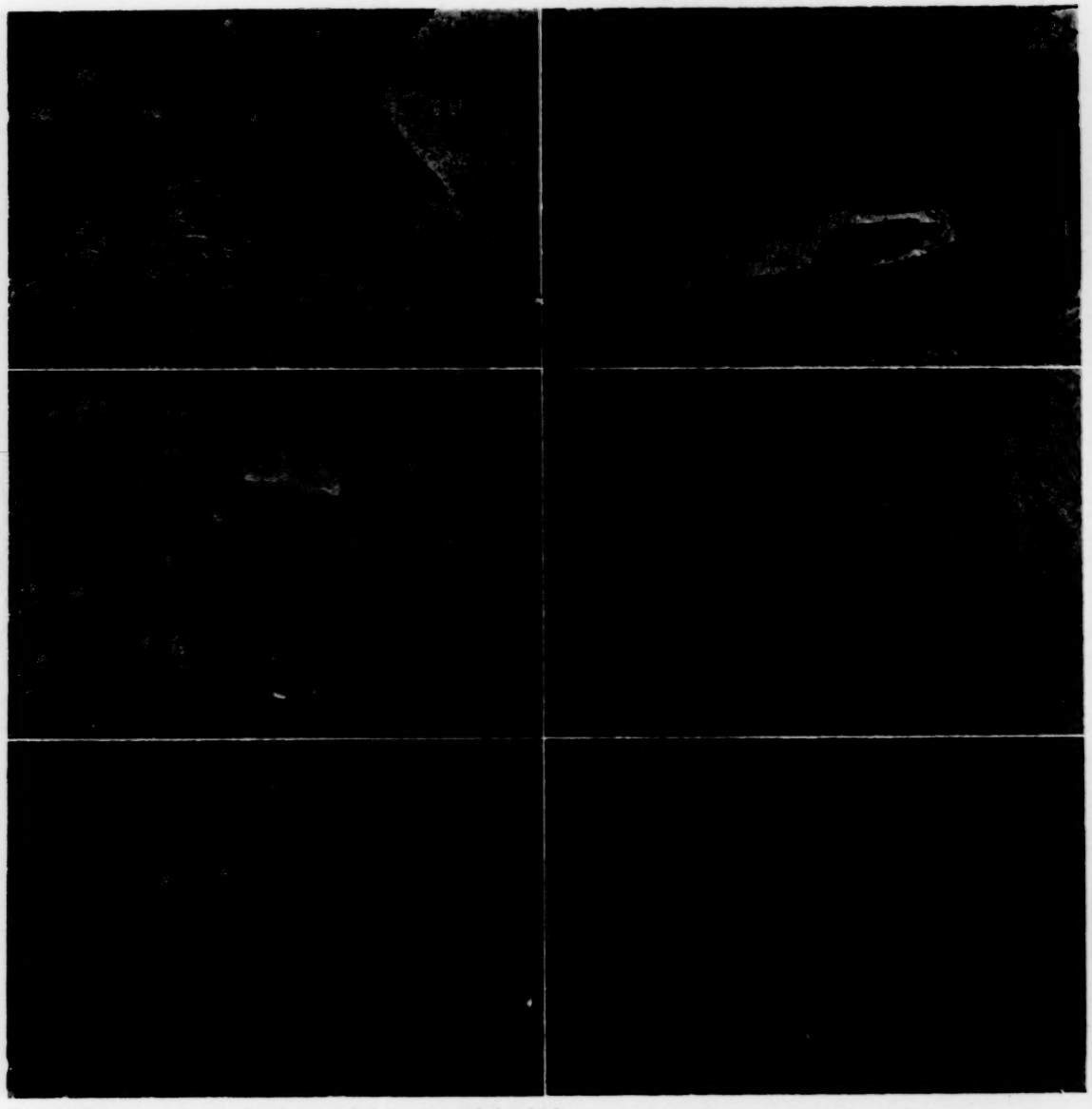


FIG. 6. Low power view of one of the scars of the kidney.
FIG. 7. Section through a branch of the renal artery. Note the intimal thickening particularly.
FIG. 8. Section of another artery. Note that the media is destroyed and that there is a fibrotic bulge which represents an obliterated aneurysm.
FIG. 9. Section through two coronary arteries. One shows intimal thickening while in the other there is complete obliteration of the lumen.
FIG. 10. Section showing small arteries in the capsule of the adrenal gland. Note obliteration of the lumens and marked adventitial fibrosis.
FIG. 11. Section of the cystic artery showing almost complete destruction of the muscularis.

total infarction. (Fig. 5.) Such a phenomenon is the anatomic change responsible for the gross observation of petechiae as well as the clinical observation of red blood cells in the urine.

From these observations it can be concluded that this patient had the malignant phase of arteriolar nephrosclerosis. Now to return to the scars which were noted in the kidneys. Figure 6 shows a low power view of one of these scars which could represent chronic pyelonephritis, as was thought on

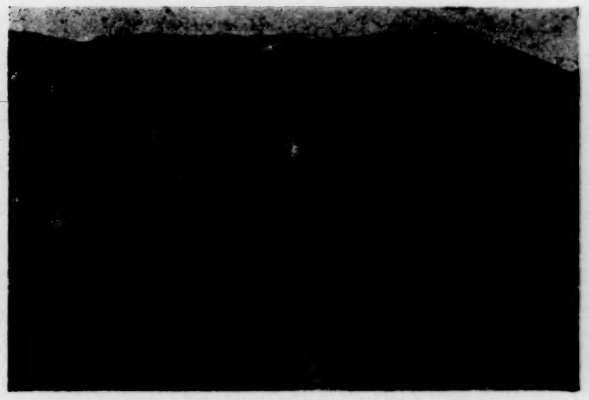


FIG. 12. Section of the liver showing an area of infarction.

the basis of the gross observations, or vascular occlusion of some type. At the base of some of the scars interesting vascular lesions are seen. If one examines a branch of the renal artery as it emerges at the pelvic region (Fig. 7), it is seen that there is tremendous thickening of the intima with a basophilic type of loose collagenous tissue. The adventitial tissue is densely fibrotic and contains a great deal of collagen. There is irregular thinning of the media as though it had been destroyed. In Figure 8, an artery is shown in which the media has completely disappeared and a local bulge which is densely fibrotic can be seen. It represents an aneurysm which has obliterated itself with periadventitial inflammation. In none of these sections is there evidence of active inflammation, but rather there is proliferation of fibroblastic tissue filling the lumen, dense collagenous tissue in the adventitia and focal destruction of the media at many points.

The heart was enlarged, weighing 430 Gm. In Fig. 9, one of the coronary arteries shows intimal thickening and in the other, there is complete obliteration of the lumen with destruction of the media, again with surrounding fibrous tissue. There is no cellular infiltration. In the small arteries in the capsule of the adrenal gland (Fig. 10) the amount of adventitial fibrosis is striking as is the almost complete obliteration of their lumens. The involvement is entirely irregular in distribution with focal lesions producing nodules which extend into the lumens. Again, there is no cellular infiltration except for occasional lymphocytes and mononuclear cells. In Figure 11 a section of the cystic artery is shown; this vessel was actually palpable at the time of autopsy. The muscularis was almost totally destroyed. Under greater magnification, proliferating fibroblasts in a loose stroma of swollen, markedly eosinophilic collagen were seen. In other words, the lesion represented fibrinoid change. In the liver, (Fig. 12) there is an infarct with much of the liver substance destroyed. Hyaline subintimal thickening of the small arteries is present. Similar changes were seen in groups of arterioles in the intestine.

To summarize these observations it is apparent that our diagnosis is healing polyarteritis nodosa. All of the anatomic changes of polyarteritis nodosa are present, particularly in the cystic artery, and also in the renal and coronary arteries. Characteristically, there is destruction of the media and aneurysmal dilatation at the point of destruction with surrounding dense fibrosis.

In reconstructing the course of the patient's illness, six months before entry to the hospital he may well have developed the lesions of polyarteritis nodosa involving the intrarenal arteries, probably with associated hypertension. During the intervening six months the arterioles throughout the body, especially those in the kidneys, exhibited sclerosing changes and finally during the last few weeks of life, the malignant phase of nephrosclerosis began and there was acute necrosis of the arterioles. It could be argued, however, that the patient originally had hypertension and developed polyarteritis later. I do not believe that there is sufficient anatomic evidence to decide whether the polyarteritis or the hypertension came first. I would like to believe that

polyarteritis was the initial lesion and that all the arteriolar lesions were secondary. The only evidence which I can cite in support of my view is that the necrotizing lesions in the kidney were most prominent and confined principally to that part of the kidney that did not have its blood supply seriously impaired. It is very difficult to find necrotizing lesions in the arterioles of the scars in the renal cortex.

The patient had bilateral apical tuberculosis with calcification. As Dr. Johnson has stated, the brain, aside from the finding of edema, was without abnormality and there was no evidence of syphilis.

DR. ALEXANDER: Is it not possible that the absence of fever was due to the fact that the lesions seen here were healing? It seems very likely that fever in periarteritis nodosa may be more common when there is active inflammation about the vessels.

DR. R. A. MOORE: We made numerous sections in an attempt to find acute periarteritic lesions but none were seen.

Final Anatomic Diagnoses: Polyarteritis nodosa, healing, involving vessels of the kidney, gallbladder, liver, heart and mediastinum; infarcts in the right lobe of the liver; arteriolar nephrosclerosis with necrosis of arterioles; arteriolar sclerosis, generalized, with minimal necrosis of arterioles; hydrothorax, bilateral; hypertrophy and dilatation of the heart; hydroperitoneum and edema of the brain.

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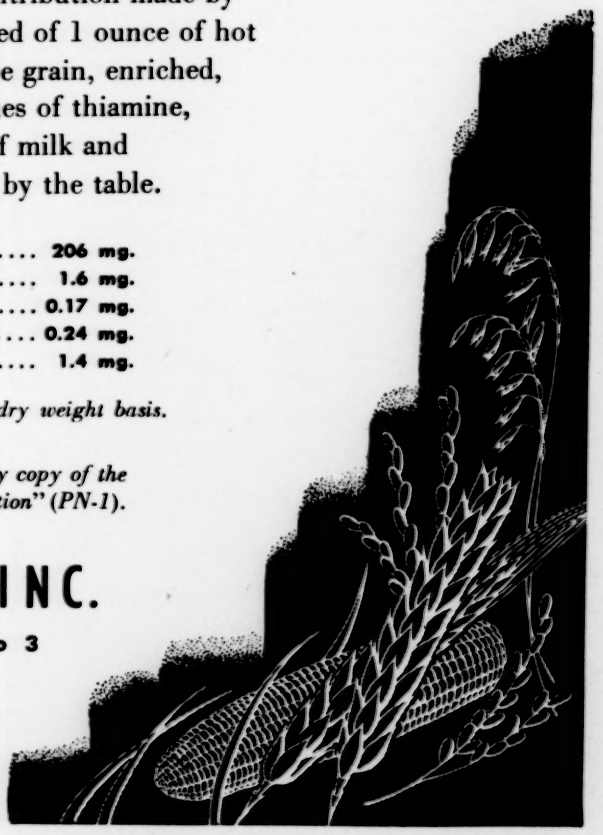

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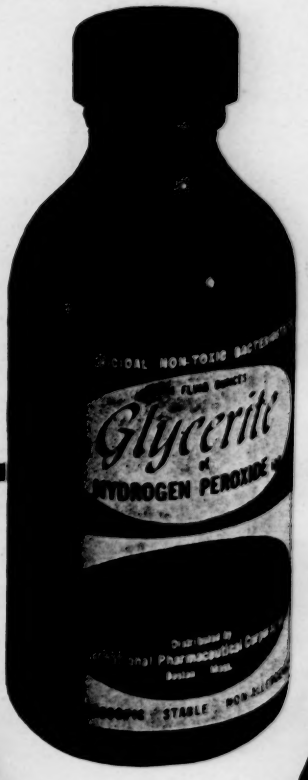

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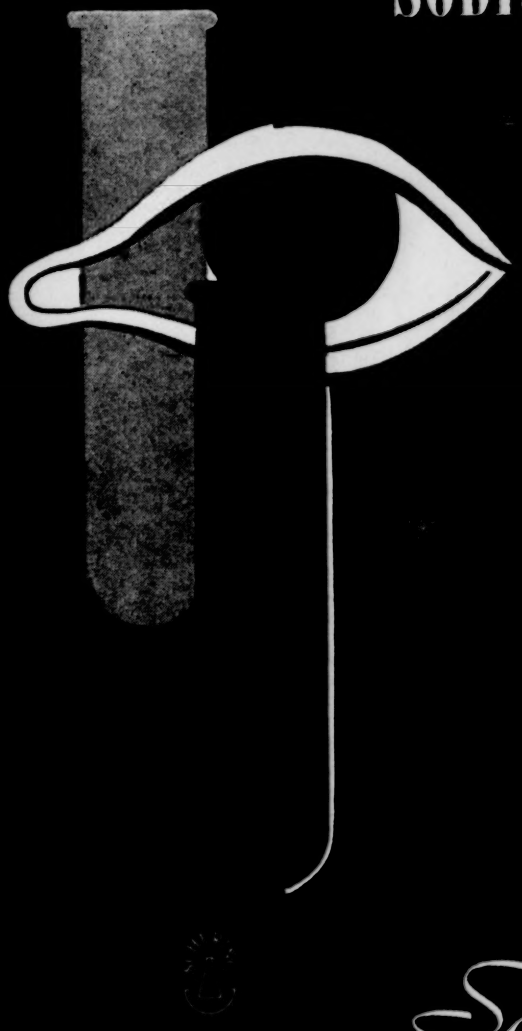

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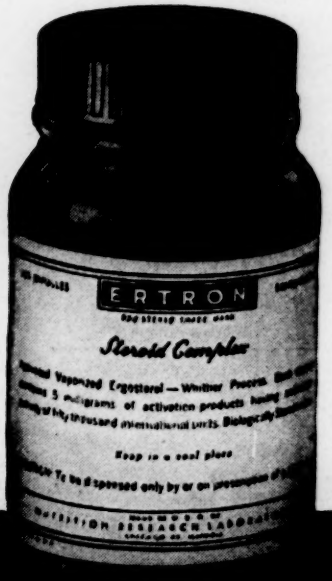

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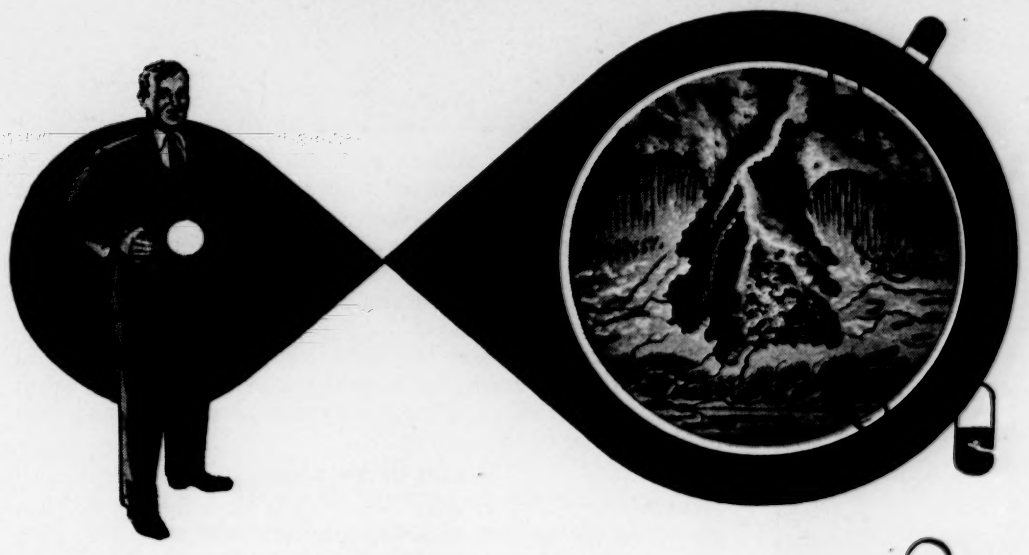

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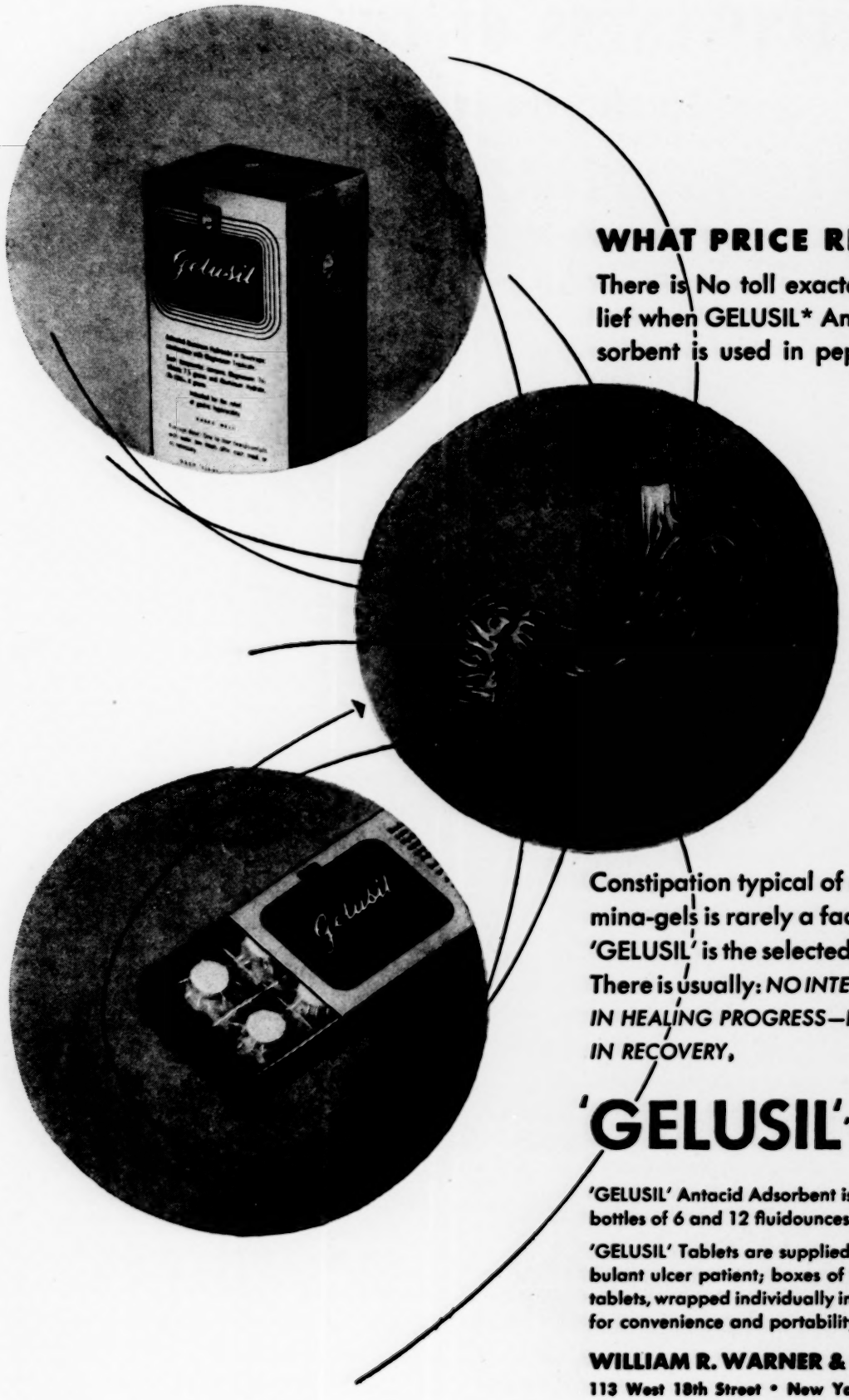

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